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Thermal characterization of the antiviral drug UC-781 and stability of its glass

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Abstract

Thermal analysis was performed on the antiviral drug UC-781, both in the crystalline and in the amorphous state using differential scanning calorimetry. Characteristic temperature parameters and kinetic parameters of crystallization were determined to assess the stability of the formed glass. Cooling of liquid UC-781 at low rate resulted into recrystallization of the drug during cooling; an amorphous product could be obtained if the cooling rate was at least 90 K min^{-1} . The T_g of this product amounted to 265.6 K when the applied heating rate was 5 K min^{-1} . The products formed at low cooling rate changed in color and texture as a result of degradation. Reheating of amorphous UC-781 through its glass transition showed two exothermic peaks whose onset and peak temperatures increased as the initial cooling rate decreased. The onset and peak temperatures of remelting of recrystallized UC-781 as well as its enthalpy of fusion generally decreased when the initial cooling rate was reduced. UC-781 glass displayed a higher stability at higher heating rates. The apparent glass transition temperature was dependent on the heating rate, and it was shown that simple first order kinetics could be used to describe the transfer from the glassy to the supercooled liquid state. The data presented in this paper indicate that both kinetic parameters of crystallization (k), and characteristic temperature parameters can be applied to assess the stability of pharmaceutical compounds which are prone to crystallization. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: UC-781; Crystallization; Differential scanning calorimetry; Glass transition; Temperature; Thermal stability

1. Introduction

The thiocarboxanilide derivative UC-781 (Fig. 1) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which has been shown to be extremely potent as an inhibitor of HIV-1 in cell culture.

UC-781 inhibits endogenous reverse transcriptase (ERT) in HIV-virions, an important factor in sexual transmission of HIV-1 infection [1]. In addition, its antiviral activity is hardly affected even in a very high concentration of human serum and this drug has a favorable resistance spectrum [2]. Therefore, this compound should be regarded as a potential candidate for the treatment of HIV-1 infected individuals. Despite the potential of this compound, its poor aqueous solubility and low dissolution rate may limit its oral absorption.

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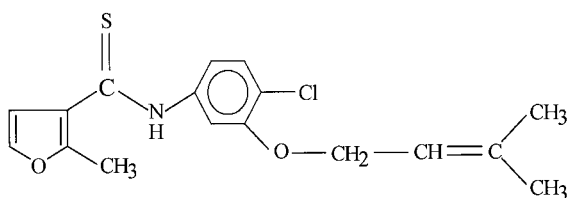


Fig. 1. Chemical structure of UC-781.

In order to overcome the dissolution-rate limited oral absorption, we have recently formulated and characterized solid dispersions of UC-781 with PEG 6000 and Gelucire 44/14 [3]. The dissolution properties of the drug were significantly improved. It was shown that pure UC-781 is highly crystalline in nature and that the carriers mentioned did not change its apparent crystalline state. On the other hand, recent investigations with polyvinylpyrrolidone (PVP K30) as a carrier indicated that the drug was completely amorphous in dispersions up to a concentration of 50% w/w [4]. For compounds whose oral absorption is limited by dissolution, amorphous compounds are preferred due to favorable dissolution properties [5], unfortunately, from a thermodynamical point of view, glassy or amorphous components are metastable with respect to the corresponding crystalline state, and a transition from the amorphous to the crystalline state as a function of time is always possible [6]. In this respect, it is important to evaluate the stability of glasses of the pure drugs and the factors that influence their crystallization.

Some parameters to predict the stability of glasses or amorphous compounds have been described in literature; among them is the use of the mean relaxation time constant and relaxation time distribution parameter [7,8]. Other parameters are described by Cheng [9], and Saad and Poulain [10], and these include a characteristic temperature criterion and the crystallization rate constant (k) of amorphous systems that are prone to recrystallization. The simplest characteristic temperature criterion is: $\Delta T = T_x - T_g$, where T_x is the onset of crystallization and T_g the glass transition temperature. Alternatively, Hruby's criterion which can also be used in the case of recrystallization is defined as $H_r = (T_p - T_g) / (T_m - T_p)$, where T_m is the melting temperature and T_p the crystallization temperature (maximum peak

temperature). Two modifications of H_r criterion have been described, i.e. H' and S ; which are defined as $H' = (T_x - T_g) / T_g$ and $S = (T_p - T_x)(T_x - T_g) / T_g$. Crystallization activation energy (E_a) can also be used to predict the stability of a glass using E_a / RT_p as the determining parameter ($R =$ molar gas constant). The higher the value of E_a / RT_p , the higher the tendency for devitrification. On the other hand, Surinach et al. [11] recommend the use of crystallization rate constant (k) because it takes into account both the activation energy (E_a) and the frequency factor or collision frequency (ν). The crystallization rate constant is therefore regarded as a good criterion for the evaluation of the stability of glasses, and it can be calculated by using the following equation: $k(T) = \nu \exp(-E_a / RT_p)$. However, due to the susceptibility of the $k(T)$ criterion to both the heating rate and temperature, some modifications of $k(T)$ have been proposed, and have been found to be useful in evaluating the stability of glasses [9]. Modifications of $k(T)$ are presented by Eqs. (1)–(3):

$$k_y(T) = \nu \exp \left[-\frac{E}{RT_p} \left(\frac{T_x - T_g}{T_m} \right) \right] \quad (1)$$

$$k_b(T) = \nu \exp \left(-\frac{E}{RT_p} \right) H_r \quad (2)$$

$$k_f(T) = \nu \exp \left[-\frac{E}{RT_p} \left(\frac{T_p - T_f}{T_f} \right) \right] \quad (3)$$

where T_f is the inflection point temperature of crystallization.

The objective of this study was to investigate the glass forming properties of UC-781 and to quantify the stability of glassy UC-781 by determination of the characteristic temperature and crystallization rate constant (k) parameters.

2. Materials and methods

2.1. Materials

UC-781 was kindly supplied by Uniroyal Chemical Company Inc. (Middlebury, CT, USA and Guelph, Ont., Canada). All other materials used in this study were of analytical or reagent grade.

2.2. Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out using a Perkin-Elmer DSC-7 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT). The instrument was operated under nitrogen purge gas at a rate of 20 ml min⁻¹.

Samples of UC-781 (1–3 mg) were analyzed in hermetically sealed aluminium pans (TA Instruments, Leatherhead, UK). The temperature calibrations were performed at each experimental heating rate using pure indium and pure water as standards, and the heat flow calibration was performed with indium as a standard. The data obtained were treated mathematically using the Pyris Software 3.03 (Perkin-Elmer, Norwalk, CT).

In order to investigate the influence of the cooling rate on the crystallization behavior of liquid UC-781, each sample of pure crystalline UC-781 was heated from 373 K at a rate of 5 K min⁻¹ to 413 K, and then cooled at different rates ranging from 100 (this was the value indicated on the apparatus) to 0.5 K min⁻¹ through its glass transition temperature (T_g) to 243 K, and then reheated at a rate of 5 K min⁻¹ to 413 K.

The influence of the heating rate on the crystallization behavior of glassy UC-781 was investigated

as follows: pure crystalline UC-781 was heated from 373 to 413 K at a rate of 5 K min⁻¹, subsequently cooled at a rate of 100 K min⁻¹ to 243 K and then reheated through its T_g to 413 K at rates of 2, 5, 10, 15, 20, and 25 K min⁻¹. The maximum crystallization peak temperature (T_p) was determined directly from the DSC reheating curves. The inflection point temperature of crystallization (T_f) was obtained from the derivative differential thermal (DDT) curves of recrystallized UC-781: DDT curves were obtained by differentiating the DSC curves and the inflection point temperature (T_f) was determined as the peak temperature on the DDT curves. Other parameters recorded were: peak temperature of melting (T_m) and onset of melting (T_o) of UC-781, glass transition temperature (T_g), and the enthalpy of fusion (ΔH_f) of crystalline UC-781.

3. Results and discussion

3.1. Influence of the cooling rate of liquid UC-781 on the thermal stability

Table 1 shows the effect of cooling the melts of UC-781 at different rates. It is interesting to note that crystallization of UC-781 is observed during cooling. As the cooling rate is reduced, the crystallization onset and peak temperatures are also relatively increased.

Table 1
Crystallization of liquid UC-781 during cooling (“cooling”) and reheating of glassy UC-781 (“Peak I” and “Peak II”)^a

Cooling rate (K min ⁻¹)	Cooling			Peak I			Peak II		
	T_x (K)	T_p (K)	ΔH_C (J g ⁻¹)	T_x (K)	T_p (K)	ΔH_C (J g ⁻¹)	T_{onset} (K)	T_p (K)	ΔH (J g ⁻¹)
100	–	–	–	297.1	300.1	51.2	323.0	332.1	9.2
90	–	–	–	293.8	299.7	48.1	323.4	330.8	6.6
80	280.7	271.4	6.2	296.7	299.8	49.7	323.2	331.2	7.9
70	297.7	282.1	9.7	296.8	299.8	48.5	323.4	331.8	8.0
60	304.5	288.8	12.0	296.5	299.5	48.3	322.5	330.9	8.8
50	303.8	294.5	9.3	296.7	300.0	46.9	323.4	331.6	7.9
40	310.9	299.5	19.5	297.0	300.2	40.4	323.5	332.2	11.3
30	318.1	307.9	51.9	295.4	299.5	14.5	330.8	340.3	11.9
20	321.1	313.4	71.8	295.0	295.4	2.7	340.0	348.6	15.4
10	323.6	321.9	73.0	–	–	–	346.6	353.0	16.8
5	326.1	321.9	73.1	–	–	–	349.9	355.1	20.1

^a Conditions: heating of crystalline UC-781 from 373 to 413 K at 5 K min⁻¹, followed by cooling at different rates to 243 K as shown in the table and subsequently reheated at a rate of 5 K min⁻¹ to 413 K, T_x : onset of crystallization, T_p : crystallization peak, and ΔH_C : enthalpy of crystallization.

The slower cooling rate appears to favor the crystallization of UC-781 during cooling since at a cooling rate of 100 and 90 K min⁻¹, there was no crystallization of UC-781 observed during cooling. This observation suggests that in order to prevent crystallization of UC-781 and other compounds with similar properties during cooling, it is important to cool the melts at very high cooling rates. The explanation for this phenomenon is based on the fact that at a higher cooling rate there is no time available for crystallization to take place.

Melting of crystalline UC-781 followed by cooling at different rates with subsequent reheating at the same rate (5 K min⁻¹) was also accompanied with crystallization of UC-781. Besides T_g at 265.6 K, two exothermic peaks were observed in the reheating step. The appearance of an exothermic peak (peak I) in this case shows that UC-781 was partially converted into a glass by cooling, but was not stable enough and recrystallized again at around 299 K. At the lower cooling rates, e.g. 5 and 10 K min⁻¹ the crystallization of UC-781 (peak I) was not observed during subsequent heating, indicating complete recrystallization during cooling. The onset and peak temperatures of the first exothermic peak (Table 1), seemed to be more or less constant but the enthalpy of crystallization clearly decreased if the cooling rate in the previous step decreased. Peak II (second exothermic transition) which was detected in all samples at all cooling rates investigated, is thought to be related to a monotropic solid–solid transition since it was an irreversible exothermic transition. However, more experiments are necessary to confirm this and these are currently ongoing. The data for this peak are also summarized in Table 1. As it can be observed from Table 1, all data for this peak have a certain pattern, i.e. the onset, peak temperatures, and its enthalpy increased as the previous cooling rate was lowered. The typical DSC curves showing the observed events at different initial cooling rates but with the same reheating rate are presented in Fig. 2. What we would like to point out here again is that, the reheating step of UC-781 was made at the same rate, i.e. 5 K min⁻¹, therefore it is clear that the initial cooling rate has an influence on the thermal events observed on the subsequent reheating step. The effect of the initial cooling rate on the properties of UC-781 peaks in the subsequent reheating steps is shown in Table 2. The peak

temperatures (T_m) of UC-781 were affected by changing the initial cooling rates, e.g. at 100 and 0.5 K min⁻¹, the peak temperature values were 401.6 and 377.3 K, respectively. The onset of remelting and enthalpy of fusion were dramatically reduced for samples whose initial cooling rates were lower, e.g. at 0.5 K min⁻¹ the enthalpy of fusion was 24.5 J g⁻¹; the enthalpy of fusion of UC-781 at a cooling rate of 100 K min⁻¹ was 116.0 J g⁻¹. The decrease in enthalpy of fusion of UC-781 suggests the distortion of its crystal lattice and/or the presence of other components (impurities). On the other hand, the glass transition temperature was not influenced by the cooling rates, but due to a high extent of recrystallization during cooling it could only be detected up to a cooling rate of 40 K min⁻¹. The reduction in enthalpy of fusion of UC-781 during the reheating step after cooling at a low rate can be explained as a result of degradation. Peak temperatures and onset of melting are also low compared to the original compound, and this can also be explained as a result of the presence of degradation products, and hence melting point depression. The broadness of the peaks after cooling the liquid drug at a low rate also suggests that the purity of the samples is low compared to the original product. In order to confirm the thermal degradation, the samples were analyzed by HPLC and spectrophotometry. The results confirmed the presence of impurities (Fig. 3), and this accounts for the lowering of peak temperatures and broadness of peaks observed in this study. It could also be noted that the color and texture of the samples obtained at the lowest cooling rates (e.g. 0.5 and 1 K min⁻¹) changed compared to those obtained at higher cooling rates. These effects increased noticeably with decreasing cooling rate probably because of prolonged residence time at higher temperatures. The degradation products act as impurities and this finally result into the melting point depression. In order to have an idea on the extent of impurity of UC-781 melts, the Van't Hoff equation (Eq. (4)) was used to calculate the purity [12]:

$$T_m = T_o - \frac{RT_o^2 x}{\Delta H_o} \frac{1}{F} \quad (4)$$

where T_m is the sample temperature at equilibrium (K), T_o the melting point of the pure sample (K), R the gas constant, x the mole fraction of impurity, and F the

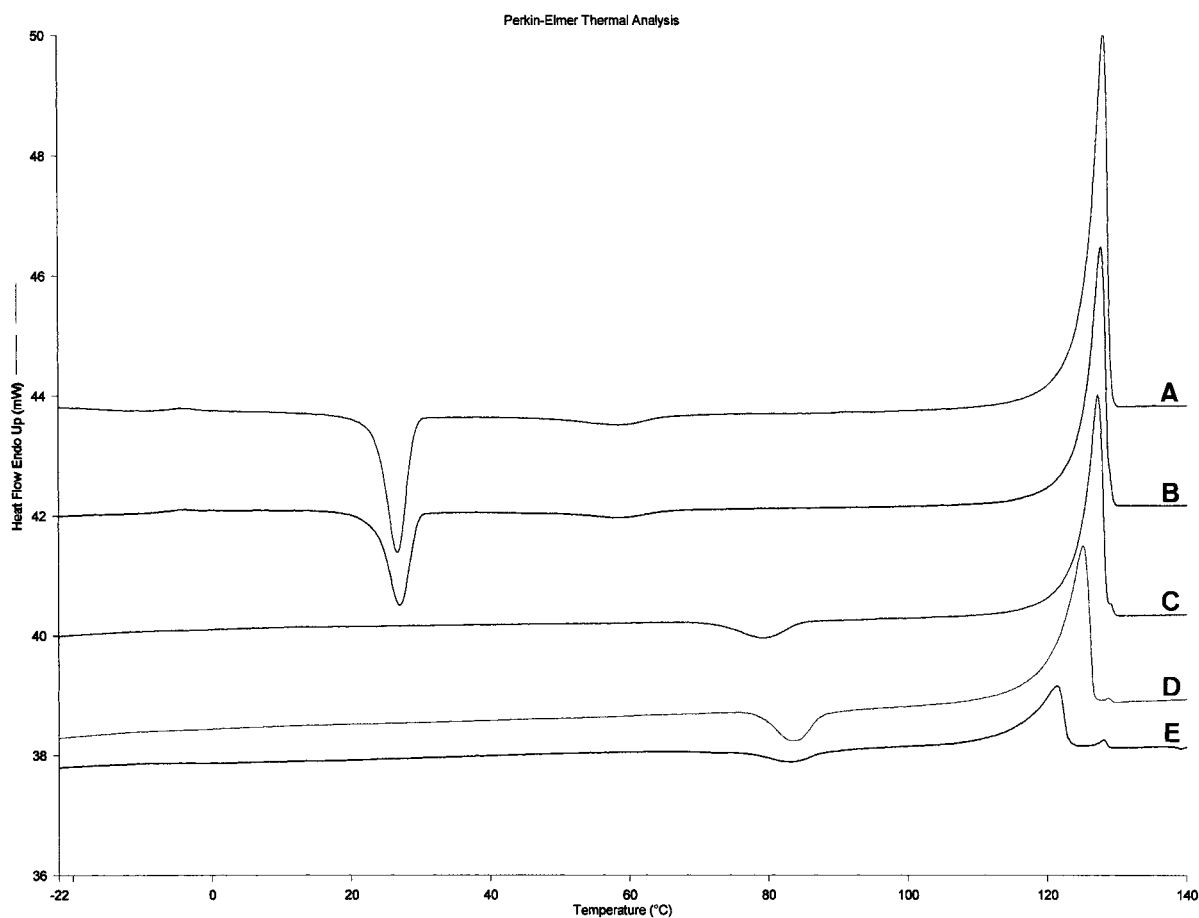


Fig. 2. DSC curves showing the effect of cooling melted UC-781 at different rates on the thermal events during reheating at the same rate. Cooling rates: curve A, 100 K min⁻¹; curve B, 50 K min⁻¹; curve C, 10 K min⁻¹; curve D, 5 K min⁻¹; and curve E, 2 K min⁻¹.

fraction of total sample melted at T_m . The above equation predicts a linear-relationship with y-intercept equal to T_o when T_m is plotted against $1/F$; x can easily be determined from the slope of this graph. However, the plot of sample temperature (T_m) against $1/F$ does not necessarily result in a straight line due to a phenomenon known as undetectable melting, and in this respect a series of corrections have to be performed until a straight line is obtained. The results obtained from this study showed that the samples obtained at lower cooling rates have a higher concentration of impurities, and in fact at a cooling rate of 0.5 K min⁻¹ the value was extremely large. The mole fraction of impurities obtained at cooling rates of 100, 50, 10 and 0.5 K min⁻¹ were 4.1, 5.4, 5.8, and

27.8 mol%, respectively. It should, however, be kept in mind that the Van't Hoff method is applicable only to samples with a low content of impurities, at least less than 2 mol% [13], and in this respect the data obtained from this experiment can only be used to give an idea on the extent of impurity.

3.2. The influence of heating rate on the stability of UC-781 glass

The influence of heating glassy UC-781 at different rates is shown in Table 3. The onset of crystallization, peak temperature of crystallization and peak melting temperature of recrystallized UC-781 increased as the heating rate was increased. At low heating rates, e.g.

Table 2
The effect of cooling rate on the peak properties of remelted UC-781^a

Cooling rate (K min ⁻¹)	Onset of remelting (K)	Remelting peak (K)	Enthalpy of remelting (J g ⁻¹)
100	400.0 ± 1.4	401.6 ± 0.4	116.0 ± 2.1
90	398.6 ± 0.6	401.0 ± 0.2	110.8 ± 6.2
80	398.3 ± 0.4	400.9 ± 0.3	110.4 ± 1.3
70	398.0 ± 0.6	400.8 ± 0.3	107.8 ± 4.8
60	398.0 ± 0.5	400.8 ± 0.3	106.8 ± 1.5
50	397.7 ± 0.3	400.6 ± 0.1	108.1 ± 5.1
40	397.9 ± 0.3	400.7 ± 0.2	111.7 ± 1.8
30	397.8 ± 0.7	400.6 ± 0.4	117.0 ± 1.1
20	397.3 ± 0.3	400.4 ± 0.2	114.5 ± 1.7
10	396.5 ± 0.7	399.8 ± 0.4	109.2 ± 6.5
5	394.3 ± 0.9	398.5 ± 0.4	102.1 ± 2.7
2	389.3 ± 1.5	393.9 ± 0.6	62.7 ± 4.5
1	380.5 ± 1.8	389.4 ± 1.5	49.3 ± 5.6
0.5	365.9 ± 2.1	377.3 ± 1.1	24.5 ± 6.1

^a Conditions: samples of melted UC-781 were reheated at a rate of 5 K min⁻¹ to 413 K. The values in parenthesis represent standard deviations ($n = 3$).

≤2 K min⁻¹, the onset and peak temperatures of all transitions (i.e. exothermic peak I, exothermic peak II, and remelting peak of UC-781) were lower (data not shown). This has been associated with the drug not having enough time to melt at higher heating rates, and this leads to a large proportion of a drug to be left in the solid state with subsequent melting afterwards. Indeed, heating samples at various rates has been regarded as an important tool in the detection of polymorphism due to the observation from other studies [14] that the polymorphic behavior of some compounds depends on the heating rate. The DSC curves obtained in this study did not show any evidence for UC-781 to have polymorphic behavior.

In a next set of experiments we investigated the influence of heating rate on the glass transition temperature. The glass transition has been considered to be a first order process from a kinetic point of view, and the relationship between the heating rate (β) and the glass transition temperature (T) can therefore be represented by the following equation [15]:

$$\ln \beta = C' - \frac{E_a}{RT} \quad (5)$$

where C' is a constant, T the apparent glass transition temperature and E_a activation energy. Fig. 4, shows a plot of log heating rate versus the reciprocal of the apparent glass transition temperature. The effect of

Table 3
Characteristic parameters of UC-781^a

β (K min ⁻¹)	T_g (K)	T_x (K)	T_p (K)	T_m (K)	T_f (K)	ΔT	H_r	H'	S	E/RT_p
25	269.0	306.2	310.2	404.9	308.1	37.1	0.43	0.14	0.55	62.9
20	268.8	304.6	308.6	404.3	306.5	35.8	0.42	0.13	0.54	63.2
15	268.7	303.5	307.2	404.2	305.3	34.8	0.40	0.13	0.49	63.5
10	267.1	300.2	303.6	403.4	302.5	33.2	0.37	0.12	0.42	64.2
5	265.6	297.1	300.1	403.1	299.1	31.5	0.33	0.12	0.35	65.0
2	263.6	294.8	297.9	402.7	296.9	31.2	0.32	0.12	0.37	65.4

^a Conditions: samples of melted UC-781 quench cooled from 413 to 243 K and then reheated at different rates to 413 K as shown in the table: β , T_g , T_x , T_p , T_m , T_f , ΔT , H_r , H' , S , and E/RT_p represent heating rate, glass transition temperature, onset of crystallization, crystallization peak temperature, melting point of UC-781, inflection point temperature, $T_p - T_x$, Hruby's criterion, modified Hruby's criterion no. 1, modified Hruby's criterion no. 2, and a criterion based on activation energy, respectively.

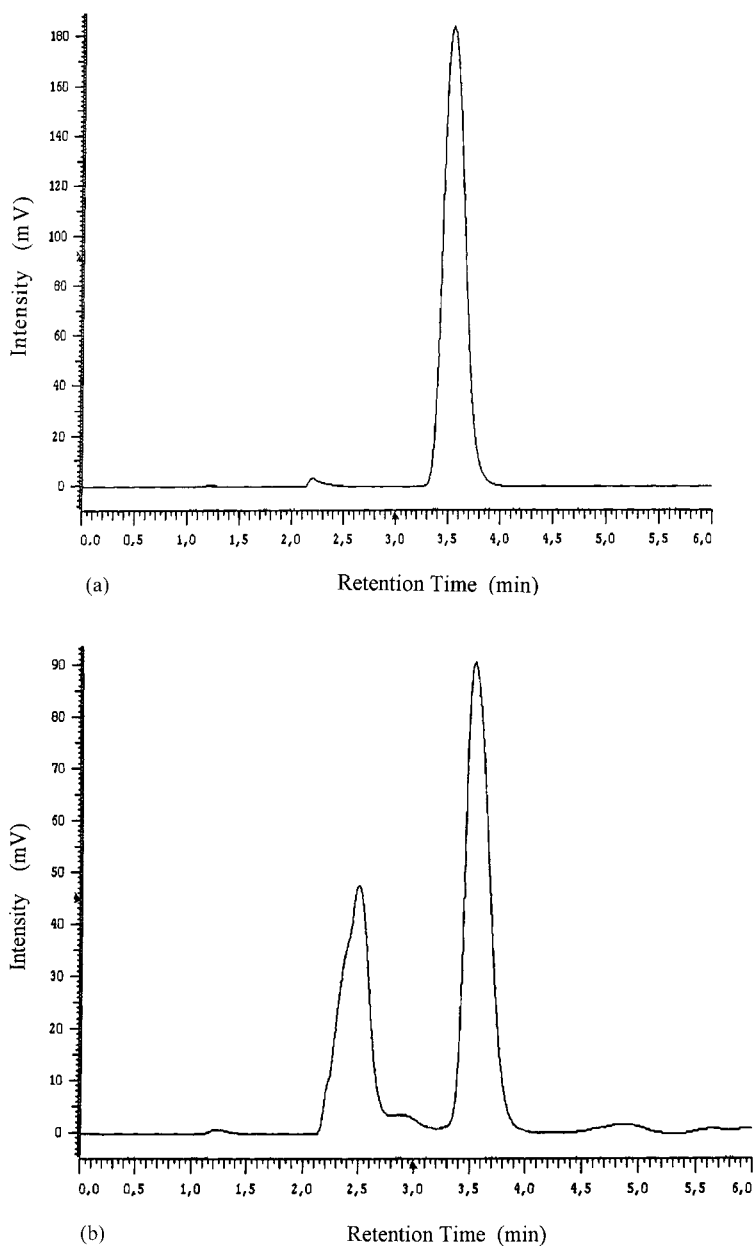


Fig. 3. Representative chromatograms of pure UC-781 (a), and melted UC-781 (b), cooled at a rate of 0.5 K min^{-1} to 243 K. The following chromatographic conditions were used; column: LiChrospher[®] 100 RP-18 ($5 \mu\text{m}$), mobile phase: acetonitrile:water (90:10 v/v), flow rate: 1 ml min^{-1} , UV detection at 297 nm.

heating rate reveals that T_{cg} increased as a function of increasing heating rate. The activation energy calculated was $257.9 \text{ kJ mol}^{-1}$. The linear behavior of this plot shows that the transformation of UC-781 from the glassy state to the supercooled liquid state can be

regarded as a simple first order conversion. The same phenomenon has been observed in other studies [16].

In order to quantitatively express the stability of glassy UC-781, characteristic temperature and crystallization rate constant (k) parameters were determined.

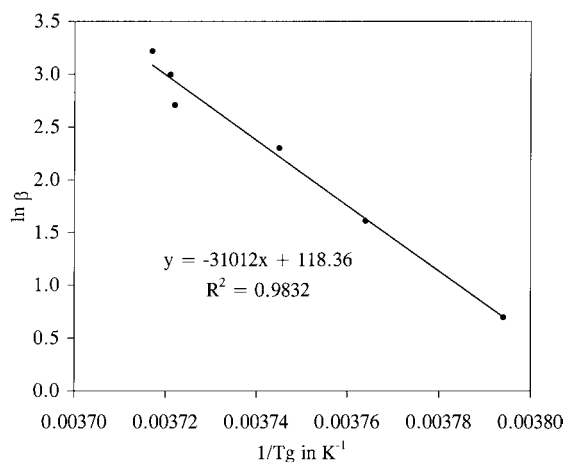


Fig. 4. Plot of log heating rate vs. reciprocal of the apparent glass transition temperature of glassy UC-781.

The data obtained from the temperature characteristic parameters are presented in Table 3. All of the characteristic temperatures parameters (i.e. ΔT , H_r , H' and S) increased with increasing heating rate, and it has been stated that the higher the parameter the greater the stability of the glass formed [9]. From the data presented in Table 3, it is evident that the glass displays higher stability at a higher heating rate compared to that at lower heating rate. On the other hand, higher values of E/RT_p indicate poor stability of the glass, which agrees with the results from the ΔT , H_r , H' and S' criteria. The explanation for this observation is similar to what we have already explained on the influence of cooling at lower rates, i.e. at a lower heating rate the sample stays at a higher temperature for a long period of time leading to a given higher degree of molecular mobility during a longer period of time, and this finally leads to the instability of the glass. In order to further quantify the stability of glassy UC-781 based on the crystallization rate constant (k), Eq. (6) was employed [9]:

$$\ln \frac{(T_f)^2}{\beta} = \frac{E_a}{RT_f} + \ln \frac{E_a}{R} - \ln \nu \quad (6)$$

In this equation T_f is the inflection point of the crystallization exotherm, E_a the activation energy, R the molar gas constant, β the heating rate, and ν the frequency factor. A plot of $\ln T_f^2/\beta$ versus $1/T_f$ is

Table 4
Kinetic parameters of crystallization for UC-781 glass^a

β (K min ⁻¹)	$k_y(T)$ (s ⁻¹)	$k_b(T)$ (s ⁻¹)	$k_f(T)$ (s ⁻¹)
25	5.66×10^{25}	2.58×10^{16}	1.19×10^{28}
20	6.69×10^{25}	6.86×10^{16}	1.17×10^{28}
15	7.66×10^{25}	1.99×10^{17}	1.21×10^{28}
10	9.14×10^{25}	1.12×10^{18}	1.42×10^{28}
5	1.126×10^{26}	6.48×10^{18}	1.43×10^{28}
2	1.128×10^{26}	8.63×10^{18}	1.42×10^{28}

^a Conditions: samples of liquid UC-781 were quench cooled from 413 to 243 K and then reheated at different rates to 413 K as shown in the table.

linear; the activation energy of crystallization and the corresponding frequency factor can be calculated from the y-intercept and the slope of the graph. Least-squares analysis of this plot showed that the activation energy (E_a) was $162.1 \text{ kJ mol}^{-1}$, and the frequency factor (ν) was $1.8 \times 10^{28} \text{ s}^{-1}$. These values were then used to calculate the crystallization rate constants based on Eqs. (1)–(3). The data obtained are presented in Table 4. The greater the value of (k) the poorer the stability of the glass. The values of k_b , k_y and k_f showed that at a lower heating rate UC-781 glass was less stable compared with the higher heating rate. These data are in agreement with the stability criteria based on the characteristic temperature parameters. The obtained crystallization rate constant parameters (i.e. $k(y)$, $k(f)$ and $k(b)$) for glassy UC-781 are very large compared to those reported for inorganic glasses like $\text{Li}_2\text{O} \cdot 2\text{SiO}_2$ and $\text{Li}_2\text{O} \cdot 1.5\text{SiO}_2$ [9]. In these materials, the crystallization rate constants were several orders of magnitude lower; indicating that UC-781 glass is very unstable compared to these compounds.

4. Conclusions

The present study has shown that cooling and heating UC-781 at different rates influence its thermal stability. At higher cooling rate liquid UC-781 did not recrystallize during cooling, and formed a glass that recrystallized following reheating. Very low cooling rates resulted in the decomposition of UC-781. The glass transition temperature was found to increase as a function of increasing heating rates. Temperature characteristic parameters and kinetic parameters of crystallization were determined to quantify the

stability of UC-781 glass. The results of this study illustrate that higher heating rates of UC-781 lead to the formation of stable glasses, while lower cooling rates lead to the degradation of UC-781.

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