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International Journal of Pharmaceutics 303 (2005) 20–30
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Kinetic study of the Maillard reaction between metoclopramide hydrochloride and lactose

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Received 25 February 2005; received in revised form 23 June 2005; accepted 23 June 2005
Available online 26 August 2005

Abstract

The purpose of this work is to study the apparent solid-state kinetics of the Maillard reaction of the colyophilized metoclopramide hydrochloride (MCP) and lactose system and to elucidate some of the effects of molecular mobility on the kinetic behavior of the amorphous mixture. Colyophilized MCP–lactose mixtures (1:9 molar ratio) were stored at temperatures ranging from 100 to 115 °C (above the glass transition temperature, T_g = 99.7 °C). This temperature range, which corresponds to the change between the glass and liquid states of the lactose–MCP mixtures, is also the temperature region where molecular mobility represents a kinetic impediment of enough significance as to affect the observed order of the reaction. A pseudo second-order kinetic model was developed to fit the MCP loss data. The proposed model gives better fit to the degradation data than many of the commonly used kinetic models available in the literature. The second-order rate constant of the model follows Arrhenius kinetics and the activation energy was found to be 53.8 kcal mol^{-1}. The molecular mobility (relaxation time) of the mixture was calculated from the heating rate dependence of the DSC-determined glass transition temperature of the mixtures. From molecular mobility considerations alone, it is possible to accurately predict the temperature dependence of the reaction rate constant. These results support the hypothesis that the solid-state reaction is mobility controlled.

Keywords: Maillard reaction; Amorphous; Molecular mobility; Reaction kinetics; Solid dispersion; Lyophilization; Mathematical model; Glass transition; Solid-state

1. Introduction

The Maillard reaction is the non-enzymatic browning reaction between a reducing sugar and an amino group. This reaction is of significance in pharmaceuticals since many drugs contain amino groups in their structure. Furthermore, lactose, a reducing sugar, is one of the most widely used pharmaceutical excipients. There are indeed many pharmaceutical products where amino compounds and lactose are both present, as a survey of the Physician's Desk Reference database would show (Fleming and Murray, 2004). The Maillard reaction in the solid state is a complex phenomenon; the physical configuration and physical properties of

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doi:10.1016/j.ijpharm.2005.06.016

the solid reactant mixture play a significant role on the kinetics of the reaction, and consequently, on the viability/shelf life of the product. The bimolecular nature of the Maillard reaction makes it an excellent model reaction for the general study of chemical reactivity in pharmaceutical solids. By following a clear marker, i.e., the disappearance of the active pharmaceutical ingredient (API), the study of this type of reaction can provide valuable information about the physical configuration of the product and about the effects of pharmaceutical processing on the observed reactivity. The Maillard reaction can be used as a probe for investigating the effects that blend properties have on drug reactivity and corresponding product stability. This information can in turn be used to improve the design of pharmaceutical processes involving solids.

The complexity of the Maillard reaction cannot be overstated (Fayle and Gerrard, 2002). Therefore, in order to extract the most meaningful information from it, it is necessary to have an experimental design over which some simplifying controls can be imposed. This report focuses on modeling the early stages of the reaction, by following the loss of the API. This represents a clear, pharmaceutically relevant probe for the progress of the reaction.

Previous investigations have primarily focused on the kinetics of the browning process in solution (Petriella et al., 1988; Stamp and Labuza, 1983; Buera et al., 1987; Baisier and Labuza, 1992), where first- or second-order kinetics are observed, depending on the concentration ratio of the two reactants, or in the solid state (Baisier and Labuza, 1992; Ge and Lee, 1997; Bell, 1996; Warmbier et al., 1976; Buera and Karel, 1995), where zero-order kinetics is typically observed. Reaction kinetics has been studied both in solution and in solid systems by following the loss of either the amine or the reducing sugar (Lee et al., 1984; Davies et al., 1997; Narayan and Cross, 1992; Bell et al., 1998b,a). In those reports, second-order reaction kinetics was observed when the amine and sugar were present in amounts with a ratio of 1:1. First-order reaction kinetics was observed for the limiting component when either the amine or the sugar was in excess (Labuza, 1994) relative to the other. It should be pointed out that agreement with simple kinetic models is obtained only during the initial stages of the reaction. This is so because as the reaction proceeds, the degradation of the intermediate products, whose chemical pathways may lead to the regeneration of the amine or further consumption of the sugar, becomes significant (Labuza and Massaro, 1990; Labuza and Baisier, 1992).

The kinetics of the reaction in the solid-state is considerably more complicated than in the case of solution phase kinetics. First, a solid system is inherently non-homogeneous, making the reaction dependent on the physical configuration of the system, not only on its composition at any given time. Second, molecules in the solid state have significantly more limited molecular mobility than molecules in solution. Hence, any of a number of factors with the ability to affect molecular mobility has the potential of becoming rate-controlling in the solid state. The apparent reaction kinetics in the solid state would therefore depend upon specific details pertaining to the physical configuration of the system. The common rate-limiting factors for solid systems are: nucleation, diffusion, water transport/content, and molecular conformation/orientation (Byrn et al., 2000). The objective of this work is to develop a kinetic model for the loss of the amine in the solid-state Maillard reaction and to investigate the influence of molecular mobility on the kinetics of the reaction. Colyophilized mixtures of metoclopramide hydrochloride (MCP) and lactose in a 1:9 (drug:sugar) molar ratio were used in this study. This enabled the study of kinetics of reaction in mixtures that started as solutions (with the drug as the limiting component of the reaction) and were subsequently turned into solid systems.

2. Materials and methods

2.1. Materials

Metoclopramide hydrochloride monohydrate, 98% purity (Fig. 1), acetic acid and tetramethylammonium hydroxide methanol (TAHM) were obtained from Sigma–Aldrich. Lactose anhydrate and acetonitrile were obtained from Mallinckrodt. The acetonitrile used was HPLC grade.

2.2. Preparation of colyophilized metoclopramide hydrochloride and lactose

A 10% (w/w) bulk aqueous solution of MCP and lactose (with 1:9 molar ratio) was prepared. One-milliliter

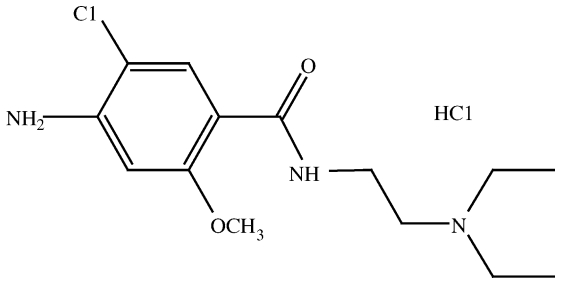

Fig. 1. Chemical structure of metoclopramide hydrochloride.

aliquots of the solution were transferred into 10-mL serum vials and kept in a Dura Stop freeze drier precooled to −40 °C for 12 h. The frozen samples were then lyophilized in the freeze dryer using a primary drying of −37 °C for 48 h, and a secondary drying of 20 °C for 12 h. The chamber pressure was maintained around 85 Pa. Samples were sealed under vacuum at the end of drying. XRPD analysis confirmed the formation of amorphous solids in the vials. Karl–Fischer titration on the freeze-dried samples gave water contents of less than 1%.

2.3. Heating rate dependency of T_g

A DSC Model 2920 (TA Instruments, New Castle, NJ) was used to carry out the glass transition temperature (T_g) measurements at heating rates of 2, 5, 10, and 20 °C min^{-1}. Indium was used to calibrate the temperature and the cell constant. About 9 mg of the amorphous sample was packed into an aluminum DSC pan, sealed, and a pinhole was made on the lid in order to allow moisture to leave the system during heating. Dry nitrogen gas was used to purge the sample chamber. The average onset temperature of three measurements was reported as the glass transition temperature. The glass transition temperature of colyophilized MCP measured at the heating rate of 10 °C min^{-1} was 99.7 ± 0.2 °C.

2.4. Solid-state Maillard reaction

The vials containing colyophilized MCP and lactose were opened in a glove box whose interior was kept at less than 10% relative humidity (RH). The vials were then quickly transferred into a desiccator containing P_2O_5 to maintain a 0% RH environment. The samples were stored at different temperatures: 100, 105, 110, and 115 °C. The temperatures used were higher than T_g because the reaction rate dramatically decreases below the glass transition temperature. Three vials were withdrawn at pre-established time intervals. HPLC was then used to quantify the amount of MCP remaining after the reaction.

2.5. HPLC

HPLC analysis was performed on a Rainin system (Varian, IL), consisting of a HPLX solvent delivery system, a Dynamax UV-D II variable wavelength UV detector, and a Dynamax AII autosampler. A 250 mm × 4.6 mm AllTech Econsphere C-18 column was used to separate the mixture. The mobile phase consisted of 70 parts of acetonitrile, 30 parts of water, and 0.2 parts of 20% (v/v) TAHM solution. The pH value of the mobile phase was adjusted to 6.5 with acetic acid. The flow rate used was 1.0 mL min^{-1}, a 10 μL injection loop was used and the detection wavelength was set at 215 nm. A sample chromatogram is shown in Fig. 2, with this analytical method, the intact API eluted at 11.7 min and the ketoseamine degradation product eluted at 3.3 min. Confirmation of the Maillard reaction between MCP hydrochloride and lactose in the solid state was verified by LC–MS. The LC–MS analysis confirmed the identity of the ketoseamine (M.W. = 624) as the compound eluting at 3.3 min (see Fig. 3).

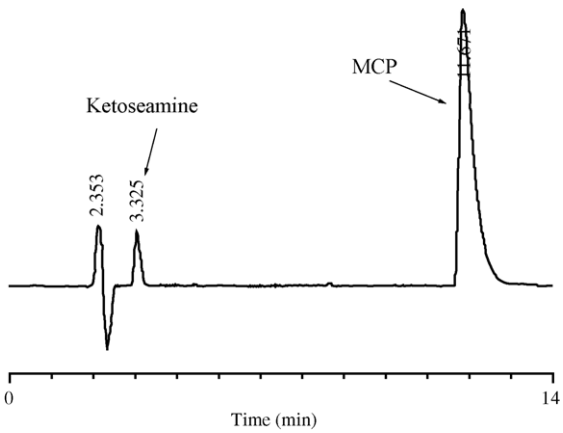

Fig. 2. Sample chormatogram of the HPLC method used in this study. The elution times for the ketoseamine derivative and the unreacted MCP were 3.3 and 11.7 min, respectively.

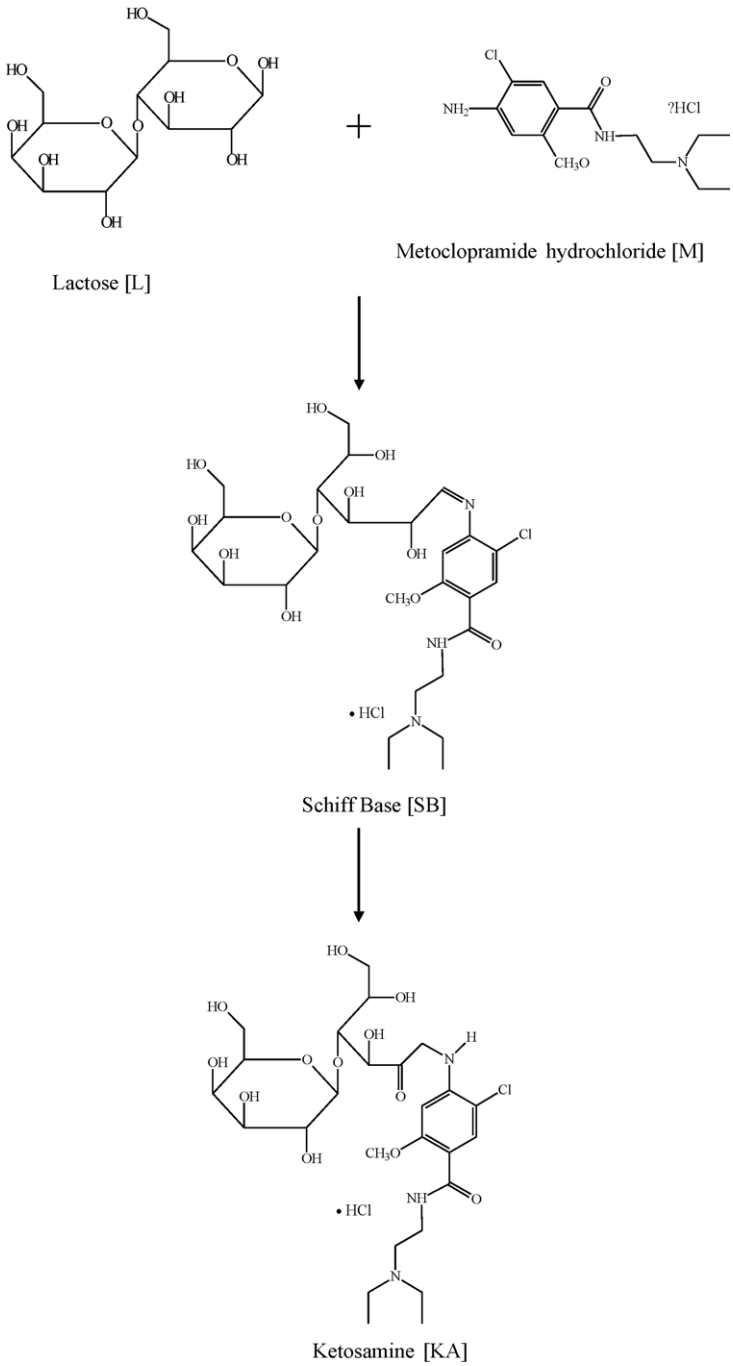

Fig. 3. Maillard reaction between metoclopramide hydrochloride and lactose.

2.6. Model development

Fig. 3 shows the reaction between MCP and lactose. The reaction can be represented on a rate law basis as follows:

$$M + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SB + H_2O \xrightarrow{k_2} KA$$

where M and L denote MCP and lactose, respectively. SB and KA are the first two intermediate products, namely the Schiff base intermediate and the ketoseamine, respectively. The terms k_1, k_{-1}, and k_2 are rate constants. For the colyophilized mixture, the reaction rates for MCP and the Schiff base can be described by the following equations:

$$-\frac{d[M]}{dt} = k_1[M][L] - k_{-1}[SB][H_2O] \quad (1)$$

$$\frac{d[SB]}{dt} = k_1[M][L] - k_{-1}[SB][H_2O] - k_2[SB] \quad (2)$$

It should be noted that the concentration of reactants and products in Eqs. (1) and (2) are unitless parameters, which are percentage values normalized to the initial (molar) amount of MCP. Since the Schiff base is unstable (Davies et al., 1997), the present model assumes that the reaction reaches a steady state with respect to the Schiff base. The concentration of SB can then be expressed as follows:

$$[SB] = \frac{k_1[M][L]}{[H_2O]k_{-1} + k_2} \quad (3)$$

Let $[M_0]$ and $[L_0]$ denote the initial concentrations of MCP and lactose, respectively, present in the colyophilized mixture. The initial concentrations and boundary conditions can then be expressed as follows:

$$t = 0, \quad [M] = [M_0],$$

$$[L] = [L_0] = n[M_0], \text{ where } n = \frac{[L_0]}{[M_0]}$$

$$t = t, \quad [M] = [M],$$

$$[L] = n[M_0] - ([M_0] - [M]) = (n-1)[M_0] + [M] \quad (4)$$

Combining Eqs. (3), (4), and (1), we obtain

$$-\frac{d[M]}{dt} = \frac{k_1k_2}{[H_2O]k_{-1} + k_2}[M]((n-1)[M_0] + [M]) \quad (5)$$

At temperatures higher than 100 °C and 0% RH, it is reasonable to assume that most of the water produced in the reaction rapidly leaves the solid phase via evaporation. Since water is being continuously produced and rapidly evaporated, the concentration of water trapped in the solid phase can be expected to be small and at steady state. From these considerations, it is possible to define $K = \frac{k_1k_2}{[H_2O]k_{-1}+k_2}$, such that the rate of the reaction can be expressed in the form

$$-\frac{d[M]}{dt} = K[M]((n-1)[M_0] + [M]) \quad (6)$$

Integration of Eq. (6), applying the boundary conditions in Eq. (4), gives the following pseudo second-order kinetic equation:

$$\ln\frac{(n-1)[M_0] + [M]}{[M]} = (n-1)[M_0]Kt + \ln n \quad (7)$$

3. Results

A plot of reaction versus time, obtained by monitoring the loss of MCP in the colyophilized samples is shown in Fig. 4. For all the temperatures tested, the MCP content exhibited a rapid initial drop followed by a decreased rate in the amine loss observed at longer times in the plot. This observation was similar to that reported in the literature (Labuza, 1994),

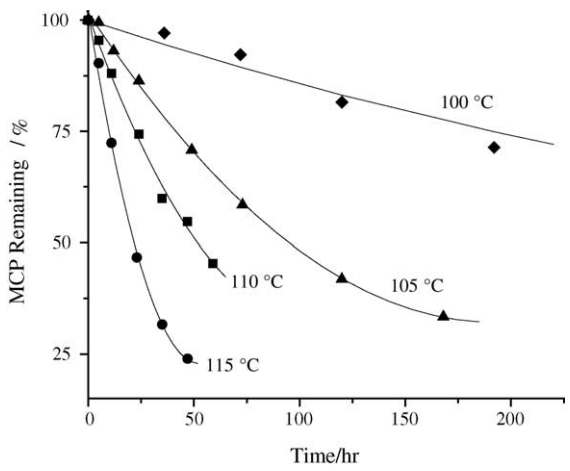

Fig. 4. Degradation profiles of amorphous metoclopramide hydrochloride–lactose mixtures via the Maillard reaction at different tempearatures. Lines are shown as visual aids.

Table 1
Statistical parameters obtained from the fitting of the reaction rate data (at 105 °C) to various solid-state kinetic models

	Slope	Intercept	Correlation (R^2)
Prout-Tompkins	0.2231	−0.8673	0.8338
Avrami-Erofe'ev			
$n = 1$	0.1646	0.0659	0.9796
$n = 2/3$	0.1431	0.6590	0.9435
$n = 1/2$	0.1267	0.3408	0.9143
$n = 1/3$	0.9930	0.1982	0.8780
$n = 1/4$	0.8110	0.5964	0.8576
$n = 1.3$	0.1707	−0.3020	0.9898
1-D phase boundary	0.1013	0.8962	0.9388
2-D phase boundary	0.0642	0.0446	0.9634
3-D phase boundary	0.0464	0.0275	0.9697
Diffusion-controlled			
1-D	0.0723	0.0251	0.9921
2-D	0.0469	0.0221	0.9876
3-D	0.0115	0.0059	0.9801
Gander	0.0139	0.0082	0.9778
Power law			
$n = 1$	0.1013	0.1038	0.9386
$n = 1/2$	0.0912	0.3490	0.8553
$n = 1/3$	0.0749	0.4994	0.8174
$n = 1/4$	0.0625	0.5952	0.7973
First-order	0.3492	−2.0629	0.7346

where the decrease in degradation rate was attributed to the regeneration of the amine when scission of the ketoseamine became significant in the latter stages of the Maillard reaction. Therefore, a common practice is to use only the initial amine-loss data when fitting the data to kinetic models. The solid-state reaction data were fitted to several kinetic models commonly used for solid-state reactions (Byrn et al., 2000). Table 1 gives a summary of the results obtained by fitting the stability data (at 105 °C) of MCP to the various solid-state kinetic models. For all the temperatures tested, none of the models gave a correlation coefficient that was consistently higher than 0.97. This is probably due to the complexity of the Maillard reaction in the solid state.

The kinetic model presented above was then used to fit the experimental data in Fig. 4. The pseudo second-order model of Eq. (7) was derived from the assumption of a steady state for the Schiff base and water. The apparent rate constant K is a function of the three micro-constants k_1, k_{-1}, and k_2 and the steady state water concentration present in the system. As can be seen

Table 2
Results from fitting the reaction rate data to the proposed pseudo second-order kinetic model (Eq. (7))

Temperature (°C)	$K \times 10^6$ (h^{-1})	R^2	Intercept
100	2.08	0.9786	2.175
105	7.96	0.9944	2.192
110	15.7	0.9936	2.183
115	37.3	0.9951	2.178

from Table 2, the proposed kinetic model gives very good correlation for all temperatures tested. In addition to the goodness of fit, Table 2 also shows that for all temperatures investigated, the value obtained for the intercept is in excellent agreement with the theoretical value of 2.197 (for $n = 9$). Based on the above results, the pseudo second-order kinetic model proposed here was substantiated for the solid-state Maillard reaction for colyophilized MCP and lactose. Fig. 5 shows that the rate constants from the model follow Arrhenius kinetics. From the figure, the activation energy for the colyophilized sample is calculated to be 53.8 kcal mol^{-1}. This value is somewhat higher than the values reported for the reaction in solution, 15–30 kcal mol^{-1} (Labuza, 1994). It is noteworthy that while in the colyophilized solid system, the Maillard reaction occurs at slower rates than in solution, the activation energy is higher for the solid system. The higher activation energy indicates a more pronounced effect of temperature on the kinetics of reaction for the

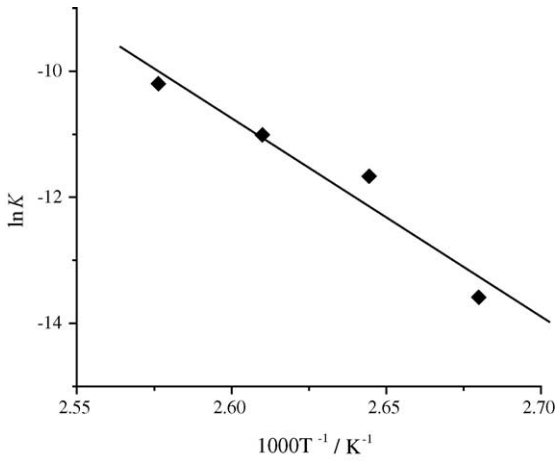

Fig. 5. Kinetics of the Maillard reaction between metoclopramide hydrochloride and lactose in the amorphous state. Arrhenius plot for the pseudo second-order rate constant (Eq. (7)).

colyophilized mixture compared with the reaction in solution. This result can be interpreted in terms of the activation of frozen modes of molecular motion in the solid. If modes of molecular motion available in solution but not in the solid state are re-activated in the colyophilized solid mixture by a raise in temperature, then a slower rate of reaction with higher activation energy would be expected for the colyophilized system.

It was previously reported that the amine loss followed first-order kinetics both in solution and in a solid mixture when the sugar is in excess (i.e., $n > 1$) (Labuza, 1994). The second-order kinetics observed here for the colyophilized mixture, despite the excess of lactose, may be due to the lower molecular mobility of the colyophilized system: a high diffusion barrier and the associated difficulty in rearranging to a favorable positioning of the reactant molecules. This point will be the subject of further discussion below.

4. Discussion

Based on the fitting results presented above, it is evident that the solid-state Maillard reaction of the colyophilized MCP and lactose is a pseudo second-order reaction, even though the lactose is present eight-fold in excess ($n = 9$) relative to the amount of MCP. Considering that the Maillard reaction follows second-order reaction kinetics only when the sugar:amine ratio, n, is equal or close to unity (Labuza, 1994), the apparent discrepancy can be explained by lower molecular mobility of MCP and lactose in the freeze-dried cake relative to a solution. The Maillard reaction is a bimolecular one; the first step involves the encounter of two molecules, one of lactose and one of MCP. In the colyophilized mixture, MCP and lactose are mixed at a molecular level, much the same as in solution. In a liquid, the thermal agitation and movement cause molecules to change immediate neighbors, thus the liquid structure, about every 10^{-10} to 10^{-11} s (Wertz, 1980). This means that in the time scales of the degradation studies, it is reasonable to assume that in the liquid phase, every lactose molecule has roughly equal probability of encountering and reacting with a MCP molecule. In other words, the relaxation time of liquid molecules is sufficiently short as to be negligible in comparison to the reaction time. However, this is not the case for the molecules in the colyophilized mixture. In this case, the probability of reaction for a given lactose molecule is very much influenced by its position relative to a MCP molecule. The viscosity in the colyophilized mixture is much higher than that of the solution. Consequently, in the colyophilizate, the ability in time of one reacting molecule to encounter (and react with) another is very much lower than in solution. Even though the lactose concentration is in excess in the colyophilized mixture, the ability of lactose molecules to encounter and subsequently react with the more scarce MCP molecules would be determined primarily by the initial local proximity between the two chemical species, rather than by their overall bulk concentrations. It is therefore the local, rather than bulk availability of the molecules to participate in the reaction that determines the rate of the Maillard reaction in the colyophilized mixture. The number of lactose molecules possessing the proper spatial position, conformation and orientation for the reaction may be far less than the total number of lactose molecules present in the mixture. In addition, owing to the limited molecular mobility in the amorphous sample, when the properly positioned molecules are consumed, it is difficult for other lactose molecules to diffuse to the reaction sites and adjust to the proper conformation for reaction. The excess in lactose concentration, although eight times higher than that of MCP, is not necessarily sufficiently mobile to be treated as a constant (condition that would lead to first-order kinetics), thus leading to the observed pseudo second-order kinetics for the reaction. Since spatial proximity between lactose and MCP molecules is a requirement for the Maillard reaction to proceed in the solid state, the effective lactose concentration (for reaction purposes) should be closer to that of MCP in the colyophilized mixture. Thus the reaction would follow a second-order kinetic profile.

The effect of water in the solid-state Maillard reaction always requires some consideration. In the treatment presented here, steady state condition is assumed for both the Schiff base and water. Under the reaction conditions used in this study (temperature higher than 100 °C and 0% RH), the water produced by the reaction can be expected to rapidly evaporate. Such a situation leads to a low, steady state concentration for water in the colyophilizate. This could also explain why, in this study, the kinetics of reaction modeled here (Eq. (7)), hold up to a point where the loss of MCP is

quite significant (see Fig. 4). Fitting of the data to the different available solid-state kinetic models listed in Table 1, was restricted to include only the initial time data. Inclusion of longer times in the fitting calculations had the effect of diminishing the goodness of fit. Conversely, the model proposed here (Eq. (7)), using the entirety of the data shown in Fig. 4, gave a better fit, including excellent agreement between the theoretical and obtained values for the intercept. The results in Table 2 summarize the fitting of the data using the proposed model. These results suggest that the fast loss of water may help delay the high chemical complexity characteristic of the Maillard reaction, observable when the reaction is at an advanced stage. It should be noted that even though the chemical effect (i.e., via the reaction rate law) of water is not of great significance given the experimental conditions of the present study, this does not necessarily trivialize the potential effects of water. Physical catalysis is an additional effect of water in the solid-state Maillard reaction (Qiu et al., in press). Therefore, the influence of diffusing water molecules produced by the reaction on the mobility (and corresponding reactivity) of lactose and/or MCP molecules is something that should not be neglected.

From the above considerations, it is important to investigate the role of molecular mobility on the Maillard reaction in the colyophilized solid mixture. Specifically, to investigate the extent to which the reaction of the colyophilized mixture, at temperatures above T_g, could be mobility controlled. It is noteworthy from Table 1 that among the different models tested, diffusion controlled models give the best fits of the data. This suggests that diffusion is an important factor for the reaction between MCP and lactose. For a mobility-controlled reaction, the reaction rate is proportional to the diffusion coefficient (Guo et al., 2000). At temperatures above T_g, the colyophilized mixture can be treated as viscous liquid where both the translational (D_t) and rotational (D_r) diffusion coefficients are considered. For a liquid molecule, the rotational relaxation is typically several orders of magnitude faster than the translational relaxation (Rice, 1985) and can be ignored. However, in highly viscous systems, where the rotational motion of a molecule may be significantly hindered, the orientation of the molecules becomes an important factor in determining the reaction rate. The Stokes–Einstein equation and the Stokes–Einstein–Debye equation are used to estimate D_t and D_r, respectively:

$$D_t = \frac{k_B T}{6\pi\eta r} \tag{8}$$

$$D_r = \frac{k_B T}{8\pi\eta r^3} \tag{9}$$

where k_B is Boltzmann constant, r the effective hydrodynamic radius of the diffusing species and η denotes viscosity. Since viscosity is proportional to relaxation time, τ (Angell, 1995), we can substitute τ for viscosity, and the reaction rate is thus inversely proportional to relaxation time:

$$\frac{k_{T_2}}{k_{T_1}} \approx \frac{D_{r_2}}{D_{r_1}} \approx \frac{T_2}{T_1}\left(\frac{\tau_1}{\tau_2}\right)^{\xi} \tag{10}$$

where ξ is a factor used to correct for difference between the experimental and calculated diffusion coefficient. A value of 0.75 was used for ξ in calculating the rate constant ratio, as suggested by Fujara et al. (1992). For temperatures above T_g, the relaxation time of supercooled indomethacin measured by the shear, dielectric, and heating rate dependence of T_g agree well within the width of their distributions (Andronis and Zografi, 1998). Based on these observations, relaxation times calculated from the heating rate dependence of T_g were used to predict the observed Arrhenius dependence of the reaction rate constant on temperature (Eq. (10)).

Fig. 6 shows the heating rate dependence of T_g of the colyophilized mixture. The method used to calculate the relaxation time is described in the Appendix A below. The calculated relaxation times at different temperatures obtained by this method are listed in Table 3. Fig. 7 shows the correlation between the experimental rate constant values and those calculated from Eq. (10). The application of Eq. (10) requires the rate constant at one reference temperature (T_1) to obtain the rate constant at any other temperature (T_2). Therefore, the applicability and value of Eq. (10) depends on its ability to properly predict the slope (Arrhenius dependence) of the reaction rate constant as a function of temperature. Fig. 7 shows very good agreement between observed and calculated temperature dependence of the rate constant. These results support the interpretation proposed for the obtained kinetic data, namely, that the Maillard reaction of the colyophilized amorphous MCP and lactose is to a good extent mobility-controlled and

Table 3
Comparison of experimental and calculated values of the degradation rate constant

Temperature (K)	τ (s)	Calculated K (h^{-1}) (Eq. (10))[a]	Calculated K (h^{-1}) (Eq. (10))[b]	Experimental K (h^{-1})
373.15	110	2.08×10^{-6}	1.57×10^{-6}	2.08×10^{-6}
378.15	25	6.51×10^{-6}	4.92×10^{-6}	7.96×10^{-6}
383.15	6	1.87×10^{-5}	1.40×10^{-5}	1.57×10^{-5}
388.15	2	4.93×10^{-5}	3.73×10^{-5}	3.73×10^{-5}

Calculated values are based on relaxation time data (Eq. (10)).
[a] Using K ($T = 100\,^{\circ}C$) as reference.
[b] Using K ($T = 115\,^{\circ}C$) as reference.

for the same reason, second-order reaction kinetics is observed even if lactose is present in excess relative to MCP.

Since molecules in solids have lower mobility than in liquids, they exhibit reaction kinetics that do not necessarily follow what would be expected from their bulk concentrations. On the other hand, the more complicated mechanism of a solid-state reaction, also implies that observed reaction kinetics may be unique to a particular solid system, i.e., different solid mixtures, physical mixture, or solid solution, are likely to exhibit different kinetics. In the case of amorphous systems (Karel and Buera, 1994), the Maillard reaction exhibits Arrhenius kinetics with two different activation energies, one value below T_g and a different one above. Typically, the activation energy is considerably higher above T_g (Karel and Buera, 1994). The results of the present study are consistent with such observations. The results presented here also indicate that there is a significant correlation between the viscosity in the amorphous matrix and the observed rate constant.

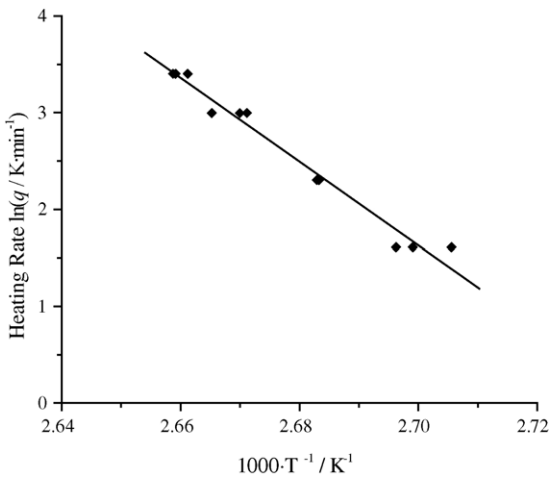

Fig. 6. Heating rate dependence of the glass transition of metoclopramide hydrochloride–lactose (1:9) colyophilized mixtures.

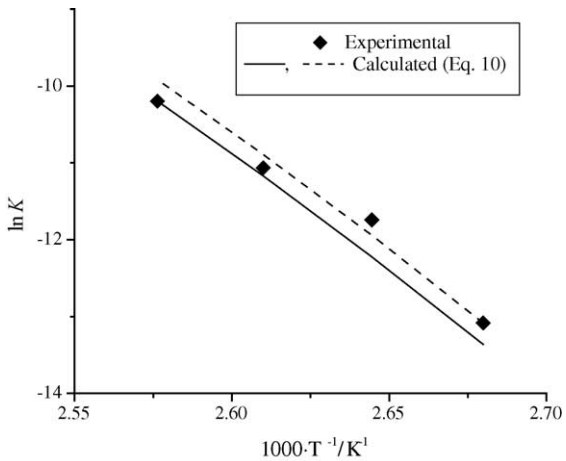

Fig. 7. Kinetic rate constant of the Maillard reaction between metoclopramide hydrochloride and lactose in the amorphous state. Comparison of experimental values with calculations based on relaxation time (Eq. (10)). Solid and dashed lines correspond reference temperatures of 100 and 115 °C, respectively.

5. Conclusion

The Maillard reaction of a freeze-dried 9:1 mixture of lactose and MCP follows second-order kinetics instead of the first-order that would be expected based on the ratio of the reactants. The obtained results show that even though one of the reactants (lactose) is in excess, its availability to participate in a bimolecular reaction is severely restricted due to the diffusion constraints of the solid state. The low molecular mobility in the solid state, combined with the molecular proximity requirement for a bimolecular reaction,

result in similar effective concentrations (for reaction purposes) of both reactants even if one is present in overall excess. In other words, the kinetics of a bimolecular reaction in a medium of limited molecular mobility does not depend on the bulk concentration of the reactants, but on the concentration of *potential* hetero-reactant *pairs* that can be formed. This condition explains the observed second-order kinetics. The proposed kinetic model correctly describes the second-order degradation profiles obtained in the temperature range 100–115 °C. This temperature window enfolds the change between the glass and liquid states for the colyophilized lactose–MCP mixtures. In other words, it is the temperature range where molecular mobility is sufficiently restricted as to affect the observed order for the reaction. The observed reaction rate constant follows Arrhenius type temperature dependence. The Arrhenius dependence can in turn be accurately predicted from molecular mobility considerations alone, as seen in Fig. 7, where the points correspond to experimentally determined rate constants but the slope of the lines were obtained, exclusively, from DSC derived relaxation data. These results strongly suggest that the reaction between lactose and MCP in the amorphous state is mobility controlled. It remains the subject of future studies to establish the extent at which molecular mobility restrictions in amorphous solids manifest themselves in the Arrhenius collision factor versus the activation energy.

Acknowledgments

This study was supported by the Purdue–Michigan Joint Program on the Physical and Chemical Stability of Pharmaceutical Solids. We are grateful to Dr. George Zografi for his discussions about the relationship between solid mobility and kinetics. We also want to thank Dr. Steven L. Nail for technical assistance in lyophilization.

Appendix A

The relaxation time of amorphous materials can be used as an indicator of their molecular mobility. For most supercooled liquids, the relaxation time can be expressed by the Vogel–Tammann–Fulcher (VTF) equation,

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right) \tag{12}$$

where τ_0 is the relaxation time at the high temperature limit, D a parameter related to the fragility of the material, and T_0 is the temperature where the relaxation time tends toward infinity. Both D and T_0 can be calculated from the slope of the plot in Fig. 6, which shows the heating rate dependence of T_g (Andronis and Zografi, 1998), as shown below.

It is assumed that in small temperature ranges, the temperature dependence of activation enthalpy for relaxation (ΔH^*) can be ignored (Ediger, 1996), and the relaxation times can be described by the Arrhenius equation:

$$\tau = \tau_0 \exp\left(\frac{\Delta H^*}{RT}\right) \tag{13}$$

Therefore, fragility (m) can be expressed by (Plazek and Ngai, 1991):

$$m = \left.\frac{\mathrm{d}(\log \tau)}{\mathrm{d}(T_g/T)}\right|_{T=T_g} = \frac{\Delta H^*|_{T_g}}{RT_g} \tag{14}$$

The activation enthalpy for relaxation (ΔH^*) can be determined from the dependence of glass transition temperature on heating rate (q) (Moynihan et al., 1974):

$$\frac{\Delta H^*}{R} = -\frac{\mathrm{d}(\ln q)}{\mathrm{d}(1/T_g)} = -(\text{slope of Fig. 6}) \tag{15}$$

The parameters D and T_0 of the VTF equation can be calculated from the fragility, m (Plazek and Ngai, 1991),

$$D = \frac{m_{\min}^2}{m - m_{\min}} \tag{16}$$

and

$$T_0 = T_g\left(1 - \frac{m_{\min}}{m}\right) \tag{17}$$

where $m_{\min} = \ln \frac{\tau_g}{\tau_0}$, which takes the value of 16, since the relaxation at T_g is usually about 100 s and τ_0 is the relaxation time at the high temperature limit, which is on the order of vibration lifetimes ($\sim 10^{-14}$ s) (Hodge, 1996).

For the colyophilized MCP and lactose, a value for ΔH^* of 361.7 kcal mol^{-1} was calculated from the slope

of Fig. 6, and m was determined as 50.67 with a T_g value of 99.7 °C, which was measured at a heating rate of 10 °C min^{-1}. The VTF parameter D and T_0 were calculated as 17.05 and 255.1 K, respectively. The relaxation times at variable temperature were calculated according to Eq. (12) and are listed in Table 3.

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