Kinetics study of hydrochlorothiazide lactose liquid state interaction using conventional isothermal arrhenius method under basic and neutral conditions

Faranak Ghaderi1,2, Mahboob Nemati1,3, Mohammad Reza Siahi-Shadbad3,4, Hadi Valizadeh5, Farnaz Monajjemzadeh4,3 *

1Food and Drug Safety Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, 2Department of Drug and Food Control, Urmia University of Medical Sciences, Urmia, Iran 3Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Tabriz, Iran, 4Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran 5Department of Pharmaceutics, Tabriz University of Medical Sciences, Tabriz, Iran

The Maillard reaction of hydrochlorothiazide (HCTZ) and lactose has been previously demonstrated in pharmaceutical formulations. In this study, the activation energy of hydrochlorothiazide and lactose interaction in the liquid state was ascertained under basic and neutral conditions. Conventional isothermal High Performance Liquid Chromatography (HPLC) technique was employed to ascertain the kinetic parameters using Arrhenius method. Results: The activation energy obtained was 82.43 and 100.28 kJ/mol under basic and neutral conditions, respectively. Consequently, it can be inferred that Maillard reaction is significantly affected by pH, which can be used as a control factor whenever the reaction potentially occurs.


INTRODUCTION

Hydrochlorothiazide, chemically known as 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide (Figure 1) is an amine containing diuretic active ingredient that is often used in the treatment of high blood pressure and swelling due to fluid build-up. For high blood pressure, it is often prescribed as a first line treatment (Carlucci et al., 2000; Chaudhary et al., 2010; McCrea et al., 1995). HCTZ may be combined with other blood pressure medications as a single tablet for optimum efficacy.

The stability of the active ingredients of drugs is affected by different factors such as the nature of the excipients used and the environmental factors such as temperature, moisture, pH and light. Any undesired change in stability can affect the quality, safety and efficacy of the drug. Stress testing is a tool for detecting possible problems that are associated with the stability of the active ingredients of a drug. It is also a tool for providing valuable data on the intrinsic stability of drug substances (Bakshi, Singh, 2002). When an incompatibility is detected in the initial steps, kinetic study would help to reveal more detailed information about the progress of the reaction.

Rate laws and rate constants are generally derived from chemical kinetic studies that involve experimental determination of reaction rate. Chemical reaction rates such as zero-order, first-order, second-order, mixed-order, or higher-order, fractional and negative order are often included. The activation energy for a reaction is usually determined experimentally using the Arrhenius equation. Reaction kinetic studies are often performed using HPLC...
(High Performance Liquid Chromatography) technique, which is highly sensitive, precise and reliable. It is however, time consuming and expensive.

In a survey, Harmon et al. (2000) characterized low levels of HCTZ–lactose condensation products that were formed by heating a wet mixture during Maillard reaction (Harmon et al., 2000). Different stability indicating HPLC methods have been reported in the determination of hydrochlorothiazide in pharmaceutical dosage forms (Lusina et al., 2005; Argekar, Sawant, 2000; Kanumula, Raman, 2000). Although degradation of HCTZ in aqueous solutions and its dependence on temperature and pH have been previously reported by Mollica, Rehm and Smith (1969), there is no kinetic assessment available for HCTZ and lactose interaction. In addition, no attention has been paid to the influence of pH on such interactions in drug molecules. Consequently, the present study was based on the kinetic assessment of HCTZ-lactose liquid state interaction using conventional isothermal Arrhenius method under basic and neutral pH conditions, which can be used as a control factor whenever the reaction potentially occurs.

**MATERIAL AND METHODS**

Material

HCTZ was obtained from Unichem (Maharashtra, India), anhydrous lactose was provided by DMV Chemical Co. (Veghal, Netherlands). HPLC grade methanol was purchased from DUKSAN (Gyeonggi-do, Korea); KH$_2$PO$_4$ and orthophosphoric acid were obtained from Merck (Darmstadt, Germany).

HPLC (High Performance Liquid Chromatography)

The Knauer HPLC system (Berlin, Germany) was made up of a Knauer controller quaternary pump and a UV detector (Knauer No. E 4310). The whole operation was controlled using EZ Chrome elite software. The HPLC method was a stability indicating method described by Bhagwate and Gaikwad (2013).

**RESULTS AND DISCUSSION**

Kinetic reaction study shows how different experimental conditions can affect the rate constant of chemical reactions. The rate constants and order of a reaction is usually obtained by experimental determinations. The order of reaction is the relationship between the concentration of reactants and the rate of a reaction. It indicates the extent to which the concentration of reactants affects the rate of reaction. The order of reaction for each reactant is often a positive whole number; however, they can sometimes be zero, fractional, mixed or negative. First-order reactions are the most common and imperative reactions in pharmaceutical reactions such as drug absorption and drug degradation (MOSS, 2013).

In zero-order reaction, the rate is independent of the concentration of the reactant and is based on equation 1 (Bett, Hall, 1968; Monajjemzadeh et al., 2014; Siahi-Shad Bad et al., 2016).

$$[C] = -kt + [C]_0 \quad \text{Equation 1}$$

The plot of $[C]$ against time was linear and the slope of the straight line was $-k$.

First-order reaction rate depends on a single reactant concentration and the value of the exponent is 1. Equation 2 corresponds to the integrated form of the first-order reaction:

$$\ln[C] = -kt + \ln[C]_0 \quad \text{Equation 2}$$

Plotting $\ln [C]$ against time for a first-order reaction gives a straight line and the value of $-k$ was computed from the slope of the straight line. The rate of reaction for a second-order reaction depends on the square of the concentration or (more commonly) on the product of two concentrations. Equation 3 corresponds to this type of reaction:

$$\frac{1}{[C]} = kt + \frac{1}{[C]_0} \quad \text{Equation 3}$$

where $C$ is the concentration of the reactant, $C_0$ is the initial concentration of the reactant, $t$ is time and $k$ is the rate constant of the reaction (Kuo, 1986).

By 1880, it was commonly known that the rate of a reaction increases with an increase in temperature; however, the reason for this phenomenon was not clear. Eventually, in 1889, the Swedish chemist Svante Arrhenius (1859-1927) combined the concepts of activation energy and the Boltzmann distribution law into one of the most valuable relationships for the dependence of reaction rates on temperature and presented the Arrhenius equation (Labuza, Riboh, 1982; Martin, Swarbrick, Cammarata, 1993).

The Arrhenius equation and the non-exponential form of this equation that is more conveniently used are presented as Equations 4 and 5:

$$k = Ae^{\frac{-E}{RT}} \quad \text{Equation 4}$$
\[ \ln k = \ln A - \frac{E}{RT} \]  

Equation 5

where A is pre-exponential factor, e is a constant, approximately 2.7281, E is the activation energy, R is the gas law constant: 8.314 J/mol-K, T is the temperature (K).

Consequently, the plotting of ln (k) against 1/T gives a straight line; the activation energy (E_a) and the pre-exponential factor (A) were obtained from the slope and the intercept of the Arrhenius plot.

In present study, the order of reaction was obtained after the residual amount of HCTZ was determined. As shown in Figure 2 and 3, the natural logarithm of a reactant concentration against time was linear in both basic and neutral conditions. The pH of the acidic and neutral samples were 13.1 and 7.1, respectively. The values of the reaction rate coefficient (k) were obtained from the slopes of the straight lines and presented in Table I. As expected, the temperature and time increased with a proportionate decrease in the HPLC peak areas.

HCTZ is an amine containing drug which can react with lactose to form Maillard reaction products (Harmon et al., 2000). In alkaline conditions, amino group present in its unionized form predominate and shows higher propensity to participate in a nucleophile reaction such as Maillard reaction (Monajjemzadeh et al., 2009; Ghaderi et al., 2016a,b; Ghaderi et al., 2015a,b).

FIGURE 2 - The first order reaction plot of HCTZ-lactose liquid mixture at pH=13.1 after 30, 60, 90 and 120 minutes incubation at 60, 70, 80 and 90 °C.

FIGURE 3 - The first order reaction plot of HCTZ-lactose liquid mixture at pH=7.1 after 30, 60, 90 and 120 minutes incubation at 60, 70, 80 and 90 °C.

TABLE I - The values of reaction rate constants (k) and RSQ obtained from the order reaction plots of HCTZ-lactose liquid mixture at pH=13.1 and 7.1 after 30, 60, 90 and 120 minutes incubation at 60, 70, 80 and 90 °C

<table>
<thead>
<tr>
<th>pH</th>
<th>Temperature (°C)</th>
<th>k</th>
<th>Mean value of RSQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Zero order reaction</td>
<td></td>
</tr>
<tr>
<td>13.1</td>
<td>60</td>
<td>6.6051E-05</td>
<td>0.9762</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>6.0768E-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>5.7051E-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>4.9519E-05</td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>60</td>
<td>3.4294E-05</td>
<td>0.9901</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>3.3273E-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>3.2677E-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>3.4051E-05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>First order reaction</td>
<td></td>
</tr>
<tr>
<td>13.1</td>
<td>60</td>
<td>0.0056</td>
<td>0.9823</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.0060</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.0064</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.0067</td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>60</td>
<td>0.0036</td>
<td>0.9905</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.0039</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.0041</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.0045</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second order reaction</td>
<td></td>
</tr>
<tr>
<td>13.1</td>
<td>60</td>
<td>0.4983</td>
<td>0.9497</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.6174</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.7425</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.9421</td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>60</td>
<td>0.4019</td>
<td>0.9837</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.4796</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.5451</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.6207</td>
<td></td>
</tr>
</tbody>
</table>
As seen in Table II, the calculated activation energy for interaction between cefadroxil and magnesium stearate (257.99±2.62kJ/mol) (Fulias et al., 2010).

The increasing effect of pH on Maillard reaction was in consonance with the available non-pharmaceutical literature data.

Abul, Haider Shipar discovered in a study that Maillard reaction under basic conditions are most feasible for the generation of the Heyns rearrangement products between dihydroxyacetone and glycine in the initial stage (Shipar, 2006).

According to our result, the activation energy obtained for HCTZ-lactose at pH 7.1 was 100.28kJ/mol, which is less than that of glibenclamide-magnesium stearate and cefadroxil-magnesium stearate mixture. This is a clear indication of a higher probability of having an incompatibility between lactose and HCTZ. In addition, the activation energy in basic condition was greater than that in neutral pH condition indicating an increase in pH effect and basic condition on the Maillard reaction.

**CONCLUSION**

Kinetic assessment of HCTZ-lactose interaction known as a drug-excipient incompatibility reaction in pharmaceutical dosage forms that was based on isothermal heating method revealed small activation energies compared to other incompatibilities mentioned in the literature. It was shown that pH has a significant effect on the progress of a nucleophilic Maillard reaction. Finally, it can be concluded that pH variations may be employed as a control factor whenever the reaction potentially occurs.

**ACKNOWLEDGEMENT**

This work is a part of a thesis for the award of PhD degree (No. 91) by Faranak Ghaderi, and is supported by the faculty of Pharmacy, Tabriz University of Medical Sciences.

**REFERENCES**


Received for publication on 26th July 2015
Accepted for publication on 03rd October 2016