Non-isothermal Kinetics Analysis of Dehydration of Lactose Monohydrate

Ravikiran A*, Arthanareeswari M, Kamaraj P, Praveen C, Pavan KV
Department of Chemistry, SRM University, Kattankulathur, Tamil Nadu, PIN 603203, India.
Email: ravianalytical@gmail.com

Abstract—**Lactose is most commonly used material in pharmaceutical industry. Anhydrous and Monohydrate forms of Lactose are well known. Lactose present in pharmaceuticals can undergo change in hydration state during different pharmaceutical processing and storage conditions. The change in hydration state may affect quality and efficacy of a pharmaceutical product in several manners. A thorough understanding of those factors affecting hydration or dehydration and the kinetics would help pharmaceutical scientists to develop products with consistent quality. In this present work an attempt is made to study non-isothermal kinetics of dehydration of Lactose monohydrate using Thermogravimetry (TG). Powder X-Ray diffraction (PXRD) and Differential Scanning Calorimeter (DSC) were used for preliminary characterization. The TG weight loss data was subjected to model-fitting kinetics analysis, total thirteen models were evaluated. Among thirteen models second order reaction found to be best explaining with a correlation of 0.9903. The Arrhenius parameters, activation energy, and pre-exponential factor were determined, the values were found to be 39.5 kcal / mol and 4.07 x 10^{20}, respectively**

Keywords-Model fitting; Kinetics; Dehydration; Thermogravimetry; Lactose Monohydrate

I. INTRODUCTION

Lactose is a disaccharide sugar derived from galactose and glucose it is most commonly used excipient in Pharmaceutical oral dosage forms. Lactose exists in different crystalline and amorphous forms [1]. Dehydration mechanism and crystallization behavior of Lactose was previously reported [2]. The transition from lactose monohydrate to anhydrous and vice a versa are most important phenomena for pharmaceutical scientists because this change in hydration state would impact physical properties [3] and potency of a blend with any drug. Thermal analysis has been used for evaluating dehydration kinetics [4-5]. Thermogravimetry (TG) is often used for non-isothermal kinetics evaluation of dehydration process [6-9]. Amount of water present in a given solid of active or inactive ingredient is important parameter which should be accurately known. Varying amount of water content can impact the potency, amount of actual drug, of a blend of final formulation. In the current study the dehydration kinetics of Lactose monohydrate was studied using non-isothermal Thermogravimetry. The basic mathematical fundamentals for kinetic models [10] were applied in this present work.

II. MATHEMATICAL-KINETICS ANALYSIS

Generally used rate equation form of solid state reactions used for isothermal analysis is

$$\frac{d\alpha}{dt} = k(T)f(\alpha) \quad (1)$$

Where α is the extent of reaction, t is the time, T is the temperature and f (α) is reaction model.

For dehydration study:

$$\alpha = \frac{w_0 - w_t}{B\, w_o} \quad (2)$$

Here w_0, w_t and B are the initial mass of the sample, the mass at time t and the fraction of weight loss for complete dehydration of the reaction, respectively. Integral form of Eq. (1) is

$$g(\alpha) = kt \quad (3)$$

$$\text{With } g(\alpha) = \int_0^{\alpha} \frac{1}{f(\alpha)} d\alpha \quad (4)$$

According to Arrhenius equation

$$k = Ae^{\frac{-Ea}{RT}} \quad (5)$$

Here k, E_a and A are rate constant, activation energy and pre-exponential factor, respectively.

From the Eq. (3) and 5, $g(\alpha)$ can be written as

$$g(\alpha) = Ae^{\frac{-Ea}{RT}} t \quad (6)$$

Under non-isothermal conditions integral form of the above equation is

$$g(\alpha) = \frac{A}{\beta}\int_0^T e^{\frac{-Ea}{RT}}\,dt \tag{7}$$

Here, β is heating rate. If $\frac{-\mathrm{Ea}}{\mathrm{RT}}$ is replaced by a variable x, the temperature integral Eq. (6) becomes.

$$g(\alpha) = \frac{AEa}{\beta R}\int_x^{\infty}\frac{e^{-x}}{x^2}\,dx \tag{8}$$

If $p(x) = \int_x^{\infty}\frac{e^{-x}}{x^2}\,dx$, then the Eq. (8) becomes

$$g(\alpha) = \frac{AEa}{\beta R}p(x) \tag{9}$$

Here, *p(x)* is the exponential integral; it has no analytical solutions but has many approximations. The Eq. (9) can be used for several model fitting methods for the analysis of non-isothermal kinetics. Model-fitting approach involves fitting different models to α-temperature curves. A model is a mathematical expression, developed based on mechanistic assumptions, transforms a solid state reaction process into a rate equation. Therefore, different rate expressions are produced from these models. In the current study popular Coats-Redfern method [11] was used in which the asymptotic series expansion for approximating the Eq. (10) is used to get the following equation:

$$ln\frac{g(\alpha)}{T^2} = ln\left[\frac{AR}{\beta Ea}\left(1-\frac{2RT}{Ea}\right)\right] - \frac{Ea}{RT} \tag{10}$$

Where, T is the mean experimental temperature. Using the Eq. (10), the values of E_a and *A* can be obtained from Slope and Intercept values respectively from the graph plotted for $\ln\frac{g(\alpha)}{T^2}$ versus $\frac{1}{T}$ for different models.

III. EXPERIMENTAL

A. Methods

1) Powder X-ray Diffraction (PXRD)

Powder x-ray diffractograms of Lactose monohydrate and Lactose anhydrous (Obtained after dehydration of Lactose monohydrate) were collected on Regaku x-ray diffractometer (Ultima). The X-ray tube was operated at a voltage of 40 kV and current of 40 mA. Each diffraction profile was collected in continuous mode and in the scan range of 3° to 45° 2θ with a step size of 0.01° 2θ and with a time per step of 0.1 sec. Top loading method was followed.

2) Differential Scanning Calorimetry (DSC)

TA's Q1000 DSC was used for recording DSC thermograms of Lactose monohydrate. Accurately weighed powder was taken into a closed aluminum pan (40 µL), heated at a programmed rate of 5° C/min in the temperature range from 25° to 300 °C under nitrogen gas flow of 50 mL/min. Empty aluminum pan was used as a reference.

3) Thermo Gravimetric Analysis (TGA)

TA's Q500 TGA was used for recording TGA thermograms of Lactose monohydrate. Accurately weighed powder was taken into a pre-cleaned platinum pan, heated at a programmed rate of 5 °C/min in the temperature range from 25° to 200 °C under nitrogen gas flow.

IV. RESULTS AND DISCUSSION

A. Solid state characterization

Lactose monohydrate and Lactose anhydrous shows distinct Powder X-Ray Diffraction patterns. Fig. 1 shows an overlay diffractogram of Lactose Monohydrate with Anhydrous Lactose. These characteristic diffractograms are helpful in determining Lactose phases qualitatively and quantitatively in a given mixture. The TG analysis results mass loss of about 4.95% w/w from about 105 to 160° C (Fig. 2), which is agreed with the theoretical value of Lactose monohydrate (5.0% w/w) for complete dehydration . The DSC thermogram of Lactose Monohydrate (Fig. 3) shows a sharp dehydration endotherm at about 145° C (peak maximum), which is agreed well with that for the dehydration step in TGA (Fig. 2) and followed by melting of anhydrous Lactose with an onset at about 211° C.

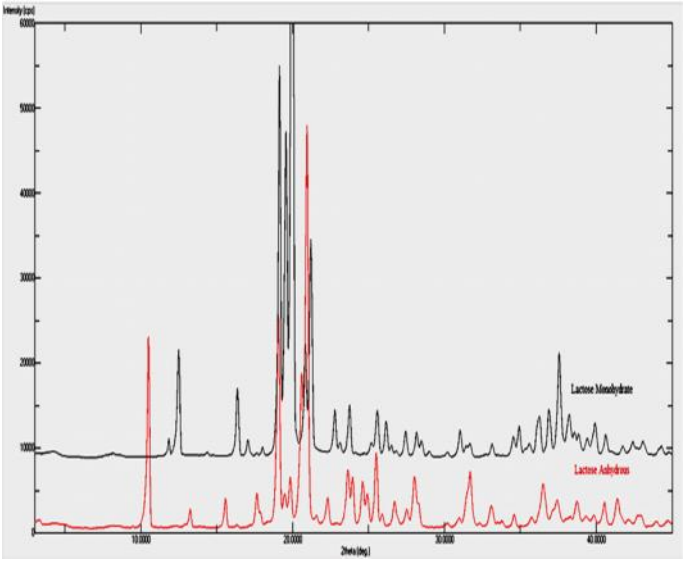

Figure 1. Powder X-Ray Diffraction overlay of Lactose Anhydrous and Lactose Monohydrate

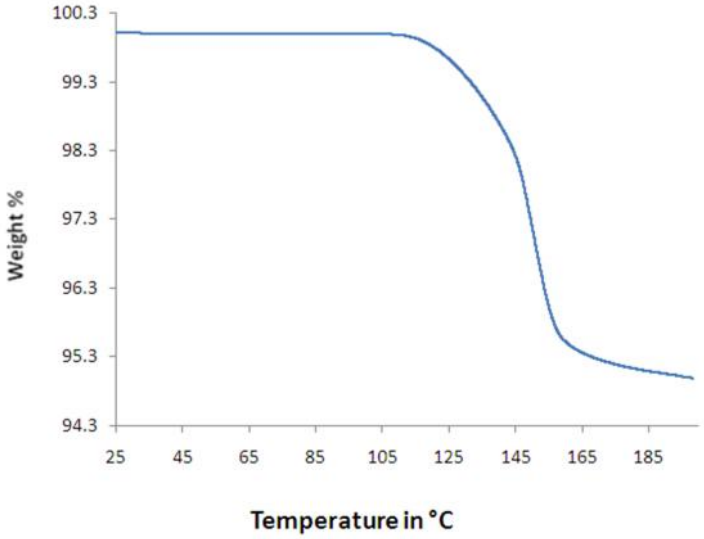

Figure 2. Thermo gravimetric analysis graph of Lactose Monohydrate

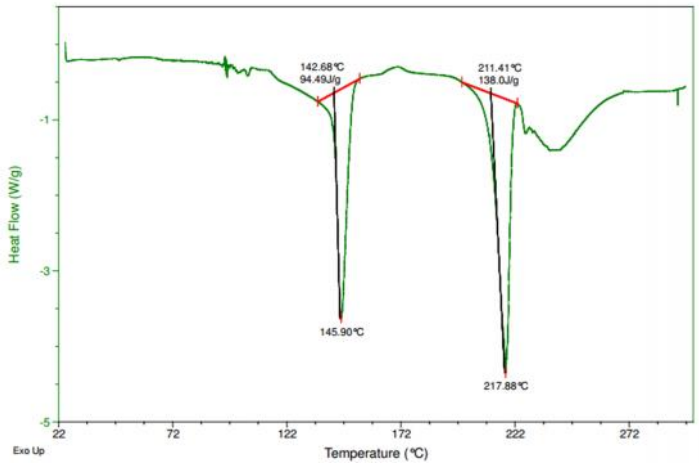

Figure 3. Differential scanning calorimetry analysis graph of Lactose Monohydrate

B. Kinetic Studies

1) Calculation of activation energy, most probable mechanism function and pre-exponential factor

Using various expressions for g (α) in Eq. (10), Arrhenius parameters were calculated from the plot of $ln\frac{g(\alpha)}{T^2}$ versus $\frac{1}{T}$ for 0<α<0.5. The set of calculated Arrhenius parameters for dehydration of Lactose monohydrate are listed in Table 1. For each model, goodness fit was determined by the correlation value, represented in Table 1. Among the different models, second order model has got maximum correlation of 0.9903. Thus this model could explain the dehydration reaction of Lactose monohydrate and the calculated activation energy and pre-exponential factor for this model were 39.5 kcal / mol and 4.07 x 10^{20} sec^{-1} respectively.

TABLE I.

(SOLID STATE REACTION MODELS USED AND ARRHENIUS PARAMETERS FOR NON-ISOTHERMAL DEHYDRATION OF LACTOSE MOMOHYDRATE USING COATS-REDFERN METHOD)

Reaction Model	**Differential form** *f(α)= 1/k dα/dt*	**Integral form** *g(α)= kt*	**Ea (kcal/mol)**	***A*** *(sec^{-1})*	***-R***
Nucleation models					
Power Law	$4\alpha^{3/4}$	`	7.7	2.42 x 10^{3}	9739
Power Law	$3\alpha^{2/3}$	$\alpha^{1/3}$	10.8	1.22 x 10^{5}	9765
Power Law	$2\alpha^{1/2}$	$\alpha^{1/2}$	16.9	2.68 x 10^{8}	9787
Avrami-Erofeev	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$	8.2	4.80 x 10^{3}	9813
Avrami-Erofeev	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$	11.4	2.99 x 10^{5}	9831
Avrami-Erofeev	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$	17.9	1.01 x 10^{9}	9846
Diffusion models					
One dimensional Diffusion	$1/2\ \alpha^{-1}$	α^{2}	72.5	3.99 x 10^{37}	9815
Diffusion control (Janders)	$2(1-\alpha)^{2/3}[1-(1-\alpha)^{1/3}]^{-1}$	$[1-(1-\alpha)^{1/3}]^{2}$	75.1	1.33 x 10^{38}	9850
Diffusion control (Crank)	$3/2[(1-\alpha)^{-1/3}-1]^{-1}$	$1-2/3\ \alpha-(1-\alpha)^{2/3}$	74.2	4.13 x 10^{37}	9838
Reaction order and geometrical contraction models					
Mampel (first order)	$1-\alpha$	$[-\ln(1-\alpha)]$	37.4	2.42 x 10^{19}	9860
Second Order	$(1-\alpha)^{2}$	$(1-\alpha)^{-1}-1$	39.5	4.07 x 10^{20}	9903
Contracting cylinder	$2(1-\alpha)^{1/2}$	$1-(1-\alpha)^{1/2}$	36.4	3.19 x 10^{18}	9834
Contracting Sphere	$3(1-\alpha)^{2/3}$	$1-(1-\alpha)^{1/3}$	36.7	3.28 x 10^{18}	9843

V. CONCLUSIONS

Our work on the dehydration kinetics of the Lactose monohydrate reveals the following characteristics.

- The mechanism of the dehydration process of lactose monohydrate is second order.
- The kinetic study of thermal dehydration of this compound was carried out by using Coats-Redfern method, which reveal that the average calculated activation energy and pre-exponential factor values are 39.5 kcal / mol and 4.07x 10^{20}, respectively.

REFERENCES

[1] K. Jouppila, J. Kansikas and Y. H. Roos, "Crystallization and X-ray Diffraction of Crystals Formed in Water-Plasticized Amorphous Lactose," Biotechnol. Progr., vol. 14, pp. 347-350, March-April 1998.

[2] S. Garnier, S. Petit and G. Coquerel, "Dehydration mechanism and crystallisation behaviour of lactose," J. Therm. Anal. Calorim., vol. 68, pp. 489-502, May 2002.

[3] C. F. Lerk, A. C. Andreae, A. H. Boer, G. K. Bolhuis, K. Zuurman, P. Hoog and J. Leverink, "Increased binding capacity and flowability of α- lactose monohydrate after dehydration," J. Pharm. Pharmacol., vol 35, pp. 747-748, November 1983.

[4] H.E. Kissinger, "Reaction kinetics in differential thermal analysis," Anal. Chem., vol 29, pp. 1702-1706, November 1957.

[5] A. Khawam, "Application of solid-state kinetics to desolvation reactions," Theses and Dissertations, *University of Iowa* , pp. 1-48, 2007.

[6] A. Ravikiran, M. Arthanareeswari, P. Kamaraj, C. Praveen and K. Pavan, "Dehydration Kinetics of Sibutramine Hydrochloride Monohydrate," Chem. Sci. Trans., vol 2(S1), pp. S288-S294, Febraury 2013.

[7] A. Ravikiran, M. Arthanareeswari, P. Kamaraj and C. Praveen, "Nonisothermal Kinetics Analysis of the dehydration of Ziprasidone Hydrochloride Monohydrate by Thermogravimetry," Indian J. Pharm. Sci., vol 75, pp. 361-364, May-June 2013.

[8] C. Praveen, M. Arthanareeswari, A. Ravikiran, P. Kamaraj and K. Pavan, "Kinetic studies on crystallization process of amorphous Vilazodone hydrochloride," Int. J. Pharm. Pharm Sci., vol 5, pp. 636-638, June 2014.

[9] D. Zhou, E.A. Schmitt, G.G.Zhang, D. Law, C.A. Wight, S. Vyazovkin and D.J. Grant, "Model-free treatment of the dehydration kinetics of nedocromil sodium trihydrate," J. Pharm. Sci., vol 92, pp. 1367-1376, July 2003.

[10] A. Khawam and D. R. Flanagan, "Solid-State Kinetic Models: Basics and Mathematical Fundamentals," J. Phys. Chem. B., vol. 110, pp. 17315-17328, August 2006.

[11] A.W. Coats and J.P. Redfern, "Kinetic parameters from thermogravimetric data," Nature, vol. 201, pp. 68 – 69, January 1964.