An investigation on thermal behaviour of Sevelamer Carbonate and non-isothermal decarboxylation kinetics using TGA to obtain activation energy and pre-exponential factor

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Abstract. Sevelamer carbonate (SC) is a phosphate binder used to treat chronic kidney disease patients to remove excess phosphate. It is an insoluble drug and thus cannot be absorbed into the systemic circulation, so the in vivo bioequivalence studies cannot be performed. The USFDA, therefore, recommends in vitro phosphate binding tests and API-sameness tests to show the interchangeability of generic variants of the sevelamer carbonate tablets. The API-sameness mentions a variety of physicochemical characteristics including carbonate content. In this work, we studied the decarboxylation characteristics using thermal techniques (DSC & TGA). We have determined the activation energy and pre-exponential factor (Arrhenius parameters- \( E_a \) and \( A \)) that of the decarboxylation using nonisothermal kinetics of decarboxylation in combination with a well-accepted Coats-Redfern model-fitting method. A total of 13 different models were tested of solid-state reaction in which the second-order model suits best with an excellent correlation of 0.9926. The resultant values of the \( E_a \) and \( A \) are 25 kcal/mol and \( 1.23007 \times 10^{12} \) Sec\(^{-1} \), respectively. The comparison of decarboxylation activation energy values may offer additional assurance on the API-sameness, in addition to comparing carbonate content alone.

1. Introduction
Sevelamer is a phosphate binder, available as hydrochloride and carbonate salt forms. Both the salt forms of sevelamer are used to treat Hyperphosphatemia (electrolyte disorder). The treatment of electrolyte disorder with sevelamer is related with a positive impact on development of vascular calcification, bone disease, and an existence advantage in some haemodialysis long-suffering populations. SC is an enhanced, buffered form of sevelamer hydrochloride developed for the hyperphosphatemia treatment in affected patients. SC holds the identical polymeric arrangement as sevelamer hydrochloride, wherein carbonate take the place of chloride as the counterion [1]. SC is chemically identified as Carbonate salt of Poly (allylamine-N, N’- diallyl-1,3-diamino-2-hydroxypropane) [2] and the structure of molecular and chemical of SC is presented in ‘Figure 1’ [3]. It is marketed as ‘Renvela’ in the tablet dosage form with 800 mg strength. As per the USFDAs draft bioequivalence (BE) guidance of sevelamer carbonate, the generics of ‘Renvela’ must meet primary criteria as API-sameness and the secondary criteria as to demonstrate the in vitro bioequivalence (phosphate-binding studies).
To prove the API-sameness, a list of characteristics is recommended by the USFDA [4], namely 1) the degree of crosslinking, 2) The degree of protonation (Carbonate content), 3) Total titratable amine, 4) Particle Size, 5) Elemental analysis, 6) Swelling index and 7) Additional characterizations (like FTIR, DSC & XRD to further characterize the physico-chemical properties of the APIs). In this present work, we focused on the carbonate part of the API. The reporting of carbonate content alone may lead to incorrect interpretation due to that value matches even if unreacted carbonates present in the material. Alternatively, the amount of activation energy ($E_a$) be able to be impacted by means of the type of carbonate and chemical environment and varies positively due to more energy required than free carbonate if present [5–8]. Hence, alongside the carbonate content, the value of $E_a$ can be a potential characteristic of the API-sameness. Sevelamer carbonate undergoes decarboxylation upon heating. Decarboxylation is an endothermic process that involves weight loss and is often accurately measured by using the thermogravimetric analyser (TGA) [9,10]. The % (w/w) of carbonate content present in sevelamer carbonate is about to 17 to 21%. Below equation-1 indicates the decarboxylation process of sevelamer carbonate upon heating

$$R-\text{NH}_3^+ \rightarrow HCO_3^- \rightarrow R-\text{NH}_2 + \text{CO}_2 + \text{H}_2\text{O}$$

TGA is an analytical technique in which the weight of a substance is continuously monitored in terms of temperature (T) and time (min) as the material undergoes a pre-defined heating process. As a result, the data acquired from the TGA experimentation is shown as a thermal curve with an vertical (y) axis having units of weight (or weight percent) and the horizontal (x) axis may be present in units with either one temperature or time[11,12]. There are many works reported on a study of dehydration kinetics using TGA weight loss data. In this present work, we studied decarboxylation kinetics using TGA weight loss data. The subsequent thermodynamic equations and various models are used to analyse sevelamer’s non-isothermal decarboxylation kinetics applying model-fitting approach.

For isothermal analysis, the rate equation for solid-state reactions is employed as

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

Where,

$\alpha$ - the extent of reaction,
$t$ - time,
$T$ - temperature
$f(\alpha)$ - reaction model [13].
The following equation is employed to know the percentage of decarboxylation:
\[ \alpha = \frac{W_0 - W_t}{B \cdot W_0} \]  
(3)

Where,
\(w_0, w_t, \) and \(B\) - Initial mass of the sample, the mass at time \((t)\) and the fraction of weight loss for complete decarboxylation of the reaction, correspondingly.

The Equation (2) Integral form is \( g(\alpha) = k t \), with
\[ g(\alpha) = \int_0^\alpha \frac{1}{ \Gamma(\alpha)} \, d\alpha. \]  
(4)

According to the Equation of Arrhenius,
\[ K = A e^{-E_a/RT} \]  
(5)

Where,
\(K\) - rate constant
\(E_a\) - the activation energy
\(A\) - the pre-exponential (frequency) factor.

\[ g(\alpha) = A e^{-E_a/RT}, \]  
(6)

Integral form of Equation (6) under non-isothermal conditions is
\[ g(\alpha) = \frac{A}{\beta} \int_0^T e^{\frac{E_a}{RT}}. \]  
(7)

Where,
\(\beta\) - the rate of heating.

When \(E_a/RT\) is substituted by \(x\) as variable, the temperature integral Equation. (7) develop into
\[ g(\alpha) = \frac{A}{\beta} \int_x^\infty \frac{e^{-x}}{x^2} \, dx \]  
(8)

When \(p(x) = \int_x^\infty \frac{e^{-x}}{x^2} \), then the Equation (8) becomes
\[ g(\alpha) = \frac{A}{\beta} p(x) \]  
(9)

where,
\(p(x)\) - the exponential integral. 
\(p(x)\) does not have analytical solutions, but it has many calculations [14–17].

The Equation. (9) can be applied for the analysis of nonisothermal kinetics by several model-fitting methods.

### Table 1. Different reaction models for Solid-State kinetic rate expressions

| Reaction model                  | \(f(\alpha)\) | \(g(\alpha)\) |
|---------------------------------|---------------|---------------|
| **Nucleation models**           |               |               |
| **Power law**                   | \(4 \alpha^{3/4}\) | \(\alpha^{1/4}\) |
| **Power law**                   | \(3 \alpha^{7/3}\) | \(\alpha^{1/3}\) |
| **Power law**                   | \(2 \alpha^{1/2}\) | \(\alpha^{1/2}\) |
| **Avrami-Erofeev**              | \(4 (1-\alpha) [-ln(1-\alpha)]^{3/4}\) | \([-ln(1-\alpha)]^{1/4}\) |
| **Avrami-Erofeev**              | \(3 (1-\alpha) [-ln(1-\alpha)]^{2/3}\) | \([-ln(1-\alpha)]^{1/3}\) |
| **Avrami-Erofeev**              | \(2 (1-\alpha) [-ln(1-\alpha)]^{1/2}\) | \([-ln(1-\alpha)]^{1/2}\) |
| **Diffusion models**            |               |               |
| **One dimensional diffusion**   | \(1/2 \alpha^{-1}\) | \(\alpha^2\) |
| **Diffusion control (Janders)** | \(2 (1-\alpha^{2/3}) [1-(1-\alpha)^{1/3}]^{-1}\) | \([1-(1-\alpha)^{1/3}]^2\) |
| **Diffusion control (Crank)**   | \(3/2(1-\alpha^{1/3})^{-1}\) | \(1-2/3 \alpha (1-\alpha)^{2/3}\) |
| **Order of Reaction and models of geometrical contraction** | | |


| Model                  | First Order Equation | Second Order Equation |
|------------------------|----------------------|-----------------------|
| Mampel (first order)   | $1 - \alpha$         | $(1 - \alpha) \ln(1 - \alpha)$ |
| Second Order           | $(1 - \alpha)^2$     | $(1 - \alpha)^{1-1}$  |
| Contracting cylinder   | $2 (1 - \alpha)^{1/2}$ | $1 - (1 - \alpha)^{1/2}$ |
| Contracting Sphere     | $3 (1 - \alpha)^{2/3}$ | $1 - (1 - \alpha)^{1/3}$ |

Model-fitting approach indicates fitting different models to $\alpha$-temperature curves. A model is a mathematical representation which is formed on the basis of mechanistic assumptions that converts solid-state reaction process into a rate equation. From these models, various representations of rates are delivered. There are four types to explain solid state reactions, (i) nucleation, (ii) geometrical contraction, (iii) diffusion, and (iv) reaction order models as per table 1[18,19].

2. Substance and methods

2.1. Substance
The Sevelamer carbonate sample was obtained from TLC pharmaceutical standards (Canada) and used, for TGA and DSC analysis. The sample was analysed using different analytical techniques without any further purification or treatment.

2.2. TGA - Thermogravimetric Analysis
The TGA experiment was performed with TGA5500-Discovery, TA Instruments. The instrument was routinely checked for its performance concerning temperature accuracy and weighing accuracy using NIST traceable calibration standards. A sample of 35.15 mg weight was placed on a pre-weighed Platinum pan. As a purge gas, Dry nitrogen (N$_2$) was used at a flow rate of 50 ml/min. The instrument was programmed to keep the samples under isothermal at 85°C for 65 min and followed by heating at 10°C / min as ramp from 85°C to 250°C. Time, temperature, as well as weight loss data were recorded.

2.3. DSC- Differential Scanning Calorimetry
The DSC experiment was completed with DSC2500-Discovery, TA Instruments. The instrument was routinely checked for its performance concerning temperature accuracy and heat-flow accuracy using NIST traceable calibration standards. 7.76 mg of Sevelamer carbonate was placed in an aluminium pan as well as sealed. As a purge gas, Dry nitrogen (N$_2$) was used at a flow rate of 50 ml/min. The instrument was programmed to heat the samples at 10°C / min as ramp from 25°C to 250°C. Temperature, as well as differential heat-flow data were recorded.

3. Consequences and Discussion

3.1. Verification of Sevelamer Carbonate by TGA and DSC
‘Figure 2’ represents the TGA thermogram of the Sevelamer Carbonate. The TGA thermogram shows two steps. In the first step, the weight loss is about 8.3% (w/w) that belongs to dehydration (water-loss) during the isothermal heating at 85°C for 65 min leaving a stable weight of about 32.22 mg. In the second step, the weight reduced from 32.22 mg (at 85°C) to 26.67 mg (at 230°C) which corresponds to a weight-loss of about 18.6% (w/w) that belongs to decarboxylation of sevelamer carbonate. DSC thermogram of Sevelamer carbonate shows two broad endothermic transitions as represented in ‘Figure 3’. The first endotherm corresponds to water-loss, the broad endotherm starts at about 43.8°C (onset) with a peak at about 86.7°C. The heat of fusion for the endothermic event is about 228.94 J/g.
Figure 2. TGA thermogram of Sevelamer carbonate that shows two types of weight-loss steps. Sevelamer carbonate being a long-chain polymer, the water-loss represents unbound or surface adsorbed kind of water, but not crystal lattice bound-type. The second endotherm corresponds to decarboxylation, the broad endotherm starts at about 131.6°C (onset) with a peak at about 170.7°C. The heat of fusion for the endothermic event is about 218.65 J/g. The presence of the two endotherms in DSC is well in agreement with the two-step weight-loss in the TGA thermogram.

Figure 3. DSC Thermogram of Sevelamer carbonate that shows two broad endothermic events.

3.2. Non-Isothermal decarboxylation analysis by TGA
The TGA data showed a total weight loss of approximately 18.6% w/w in the temperature scale from around 88 to 240°C and it was also observed that the fraction of extent of reaction was reached 0.5 at about 160°C. It is well understood that the Coats-Redfern method [20–23] in which Poincaré expansion for approximating Equation (9) is used to obtain the resulting equation:
\[
\ln \frac{g(\alpha)}{T^2} = \ln \left[ \frac{AR}{\beta E_a} \left( 1 - \frac{2RT}{E_a} \right) \right] - \frac{E_a}{RT} \tag{10}
\]

where,

- \( T \) - the average experimental temperature.

Make Use Of this Equation. \( (10) \), the values of activation energy \( (E_a) \) and pre-exponential factor \( (A) \) are obtained from the slope and intercept values, correspondingly.

From the graph plotted for various models for \( \ln \frac{g(\alpha)}{T^2} \) versus \( 1/T \), as depicted in table 2 and 'Figure 4'.

The set of Arrhenius parameters evaluated for the decarboxylation of sevelamer carbonate is listed for each model, integrity of fit was established by the correlation coefficient value, as stated in table 2. All models have a resultant correlation greater than 0.91. The first six models of solid state reaction have insignificant pre-exponential factor values that demonstrates that these models could not describe the kinetic reaction. The second order (geometrical contraction model) has a maximum correlation of 0.9926 among the remaining models.

**Table 2.** The assessed reaction models of solid state and related processed values of Arrhenius parameters for the decarboxylation kinetics of sevelamer carbonate

| Reaction model                  | f(\(\alpha\)) | g(\(\alpha\)) | \(E_a\) (kcal/mol) | A            | R          |
|---------------------------------|---------------|---------------|-------------------|--------------|------------|
| **Nucleation models**           |               |               |                   |              |            |
| Power law                       | \(4\alpha^{3/4}\) | \(\alpha^{1/4}\) | 3                 | 6.71         | 0.9161     |
| Power law                       | \(3\alpha^{2/3}\) | \(\alpha^{1/3}\) | 5                 | 4.79 \times 10^1 | 0.9328 |
| Power law                       | \(2\alpha^{1/2}\) | \(\alpha^{1/2}\) | 8                 | 2.67 \times 10^3 | 0.9453 |
| Avrami-Erofeev \(4(1-\alpha)[\ln(1-\alpha)]^{3/4}\) | \(-\ln(1-\alpha)^{1/4}\) | 4 | 1.65 \times 10^1 | 0.9598 |
| Avrami-Erofeev \(3(1-\alpha)[\ln(1-\alpha)]^{2/3}\) | \(-\ln(1-\alpha)^{1/3}\) | 6 | 1.68 \times 10^2 | 0.9673 |
| Avrami-Erofeev \(2(1-\alpha)[\ln(1-\alpha)]^{1/2}\) | \(-\ln(1-\alpha)^{1/2}\) | 10 | 1.70 \times 10^4 | 0.9730 |
| **Diffusion models**            |               |               |                   |              |            |
| One dimensional diffusion       | \(1/2 \alpha^{1/2} - 2(1-\alpha)^{1/2}\) | \(\alpha^{1/2}\) | 39 | 2.81 \times 10^{18} | 0.9588 |
| Diffusion control (Janders)     | \([1-(1-\alpha)^{1/2}]^{-1}\) | \([1-(1-\alpha)^{1/2}]^{-1}\) | 42 | 2.84 \times 10^{19} | 0.9729 |
| Diffusion control (Crank)       | \((3/2)[(1-\alpha^{1/3})^{-1}]^{-1}\) | \([1-(1-\alpha^{1/3})^{-1}]^{-1}\) | 41 | 5.52 \times 10^{18} | 0.9682 |
| **Reaction order and geometrical contraction models** | | | | |
| Mampel (first order)            | \(1-\alpha\) | \([-\ln(1-\alpha)]\) | 21 | 1.23 \times 10^{10} | 0.9774 |
| Second Order                    | \((1-\alpha)^2\) | \((1-\alpha)^{-1}\) | 25 | 1.23 \times 10^{12} | 0.9926 |
| Contracting cylinder            | \(2(1-\alpha)^{1/2}\) | \((1-\alpha)^{1/2}\) | 20 | 9.01 \times 10^8 | 0.9667 |
| Contracting Sphere              | \(3(1-\alpha)^{2/3}\) | \((1-\alpha)^{1/3}\) | 20 | 1.11 \times 10^9 | 0.9704 |
Conclusions.
In this study, the $E_a$ value corresponds to the decarboxylation of Sevelamer Carbonate was for the first time experimentally determined in solid-state using thermal analysis. TGA and DSC have been used to investigate thermal behaviour and to determine the value of $E_a$. TGA thermal analysis of Sevelamer Carbonate presents two weight-loss events in which the first is dehydration event, while the second is a decarboxylation. The TGA data were subjected to non-isothermal kinetics analysis and model fitting firstly to determine the best-fit model (second order and geometrical contraction with a correlation of 0.9926) and secondly to determine the $E_a$ value (25 kcal/mol) of the decarboxylation. As the API-sameness is an important aspect when it comes to APIs with complex molecular structure like Sevelamer carbonate, $E_a$ data can provide better reliance on the interchangeability of a generic version with its originator, as another API-sameness parameter. This can be important because $E_a$ value has a direct relationship with the nature of carbonate and its chemical environment. Due to the simplicity in TGA experimentation, it can be a potential tool for the determination of activation energy and thereby checking sameness of complex structured carbonate-containing generic API with that of its reference.

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