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Thermogravimetric Analysis and Decomposition Kinetics of Velpatasvir Co-povidone Under Non-isothermal Conditions

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Abstract

The thermal decomposition of velpatasvir:copovidone (1:1) was studied by the simultaneous thermogravimetry/derivative thermogravimetry (TG/DTG). The influence of the heating rate (10 ^{o}C min^{-1}) on the TG was verified. For the determination of kinetic parameters from the TG/DTG curves, the following methods were utilized: Arrhenius equation, Horwitz–Metzger, and Coats–Redfern methods. The kinetic studies of velpatasvir copovidone showed a thermal behaviour characteristic of first order according to the activation energy. The activation energy obtained was found to be about 99.93±9.09 kJ mol^{-1}. The TGA/DTG curves demonstrate that the drug undergoes two phases of thermal decomposition. The first is due to the dehydration of copovidone. The second phase occurs at three thermal decomposition steps. The first thermal decomposition step occurred at an interval of 210.0–407.0 ^{o}C. The second thermal decomposition step occurs in the interval of 407.0–465.0 ^{o}C. The third thermal decomposition step occurs in the interval of 465.0–621.0 ^{o}C, which may be attributed to the complete thermal decomposition.

Keywords: Velpatasvir; Copovidone; Kinetic parameters; Non-isothermal; TG/DTG.

1. Introduction

Thermal analysis is a group of techniques in which a physical property of a substance and/or its reaction products is measured as a function of temperature, whilst the substance is subjected to a controlled temperature program. Thermal analysis is an analytical, quantitative, and comparative method capable of producing fast and reproducible results. These methods are widely used in industrial products such as polymers, metals, pharmaceuticals, and minerals for quality control and research. Methods provide important information about the physical properties of materials (stability, compatibility, polymorphism, kinetic analysis…etc). These methods include thermogravimetric and thermogravimetric

derivative analysis (TG/DTG). In TG/DTG analysis, the mass of a sample in a controlled atmosphere is recorded continuously as a function of temperature or time as the temperature of the sample is increased (usually linearly with time). TG analysis is commonly employed in research and quality control testing to determine characteristics of materials such as polymers, thermal degradation (decomposition), absorbed moisture content of materials, level of inorganic and organic components in materials, decomposition points of explosives, and solvent residues (Giron, 1986). The kinetic parameters (activation energy, frequency factor, and reaction order) can be measured by thermoanalytical methods according to the progress of reactions (Coats & Redfern, 1964; Horowitz & Metzger, 1963; Logan, 1982). The present work reports studies of the thermal stability and non-isothermal kinetics of velpatasvir:copovidone (1:1). In the literature, no reports have been found for the application of TG/DTG analysis for the thermal decomposition of velpatasvir:copovidone (1:1) in drug substances and products. Therefore, the objective of this study was to investigate the thermal stability and kinetic parameters of the studied drug.

2. Experimental

2.1. Apparatus and Software

TG/DTG curves of drug substances were recorded using the Shimadzu thermogravimetric analyzer DTG-60 H (Tokyo – Japan), with TA 60 software in a dry nitrogen atmosphere at a flow rate of 40 mL min^{-1} in a platinum crucible with an empty platinum crucible as a reference. The experiments were carried out from room temperature to 800 ^{o}C at a heating rate of 10 ^{o}C min^{-1}. The sample mass was about 7.225 mg of the drug without any further treatment.

The kinetic parameters of decomposition, such as activation energy (Ea), frequency factor (A), and reaction order (n), were calculated from TGA/DTG curves. The mathematical models of the Arrhenius equation (AE) (Logan, 1982), Horowitz-Metzger (HM) (Horowitz & Metzger, 1963), and Coats-Redfern (CR) (Coats & Redfern, 1964) were used for the determination of kinetic parameters.

2.2. Samples

Velpatasvir: copovidone (1:1) was kindly supplied by Sigma Pharmaceutical Industry, Quesna, Egypt.

3. Results and Discussion:

3.1.Thermal characterization of velpatasvir / copovidone

The drugs' (TG/DTG) curves are included in the thermal analysis data displayed in Figure 1. Scheme 1 shows the weight losses and chemical alterations caused by the drug's thermal degradation. The TGA/DTG curves demonstrated that, the drug undergoes two phases of thermal decomposition. The first is due to the dehydration of copovidone with a mass loss (Δm = 0.747%) in the temperature range of 41.30–210.00 ^{o}C (Bettinetti, Bruni, Giordano, & Mura, 1994; Lopes, Catelani, Nascimento, Garcia, & Trevisan, 2020). The second phase occurs at three thermal decomposition steps. The first thermal decomposition step occurred at an interval of 210.0–407.0 ^{o}C (DTG_{max}: 317.51 °C) with Δm = 36.097% (36.583%, calculated), which may be attributed to the loss of $C_7H_{12}NO_3^{\bullet}$, $C_{10}H_{10}NO_3^{\bullet}$,

and $C_2H_5O^{\bullet}$ molecules. The second thermal decomposition step occurs in the interval of 407.0–465.0 ºC (DTG_{max}: 426.06 °C) with Δm = 18.422% (18.258%, calculated), suggesting the loss of copovidone molecules (Lopes et al., 2020). The third thermal decomposition step occurs in the interval of 465.0–621.0 ºC (DTG_{max}: 561.62 °C) with Δm = 44.734% (45.136%, calculated), which may be attributed to the complete thermal decomposition.

3.2. Kinetic analysis:

In the present study, the kinetic parameters obtained from the first thermal decomposition step were activation energy (Ea or E*), frequency factor (A), reaction order (n), and correlation coefficient (R).

3.3. Arrhenius Equation Method:

The kinetics of the main thermal decomposition steps of velpatasvir:copovidone were studied using Arrhenius equation (Logan, 1982). The computation of the kinetic parameters was based on the use of Arrhenius equation applied to the solid-state reactions. The logarithmic form of Arrhenius equation is:

LnK = LnA – Ea/ RT……..(1)

Arrhenius equation can be combined with the rate equation, which is written as:

dα/dt = K(T) f(α)……....(2)

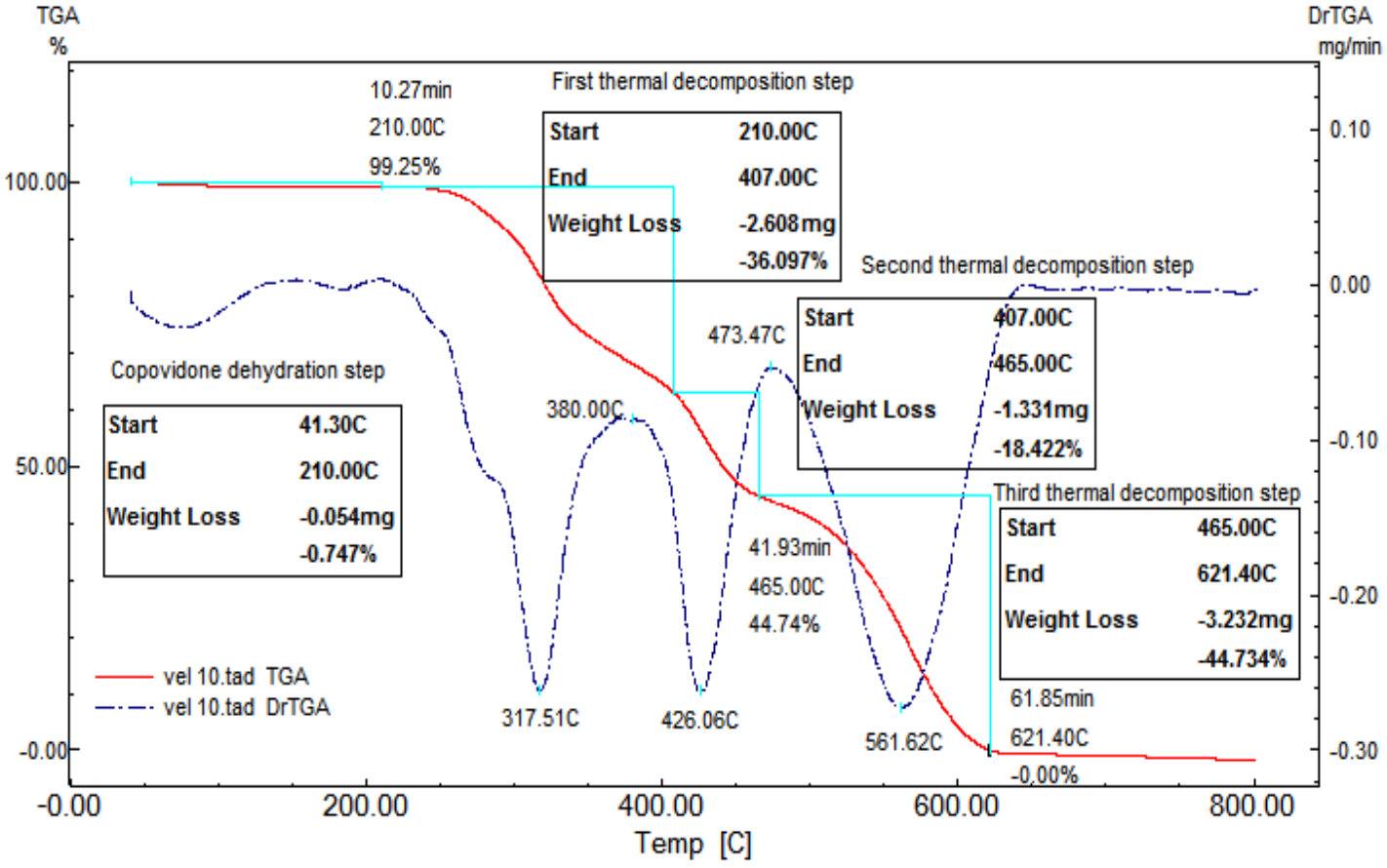
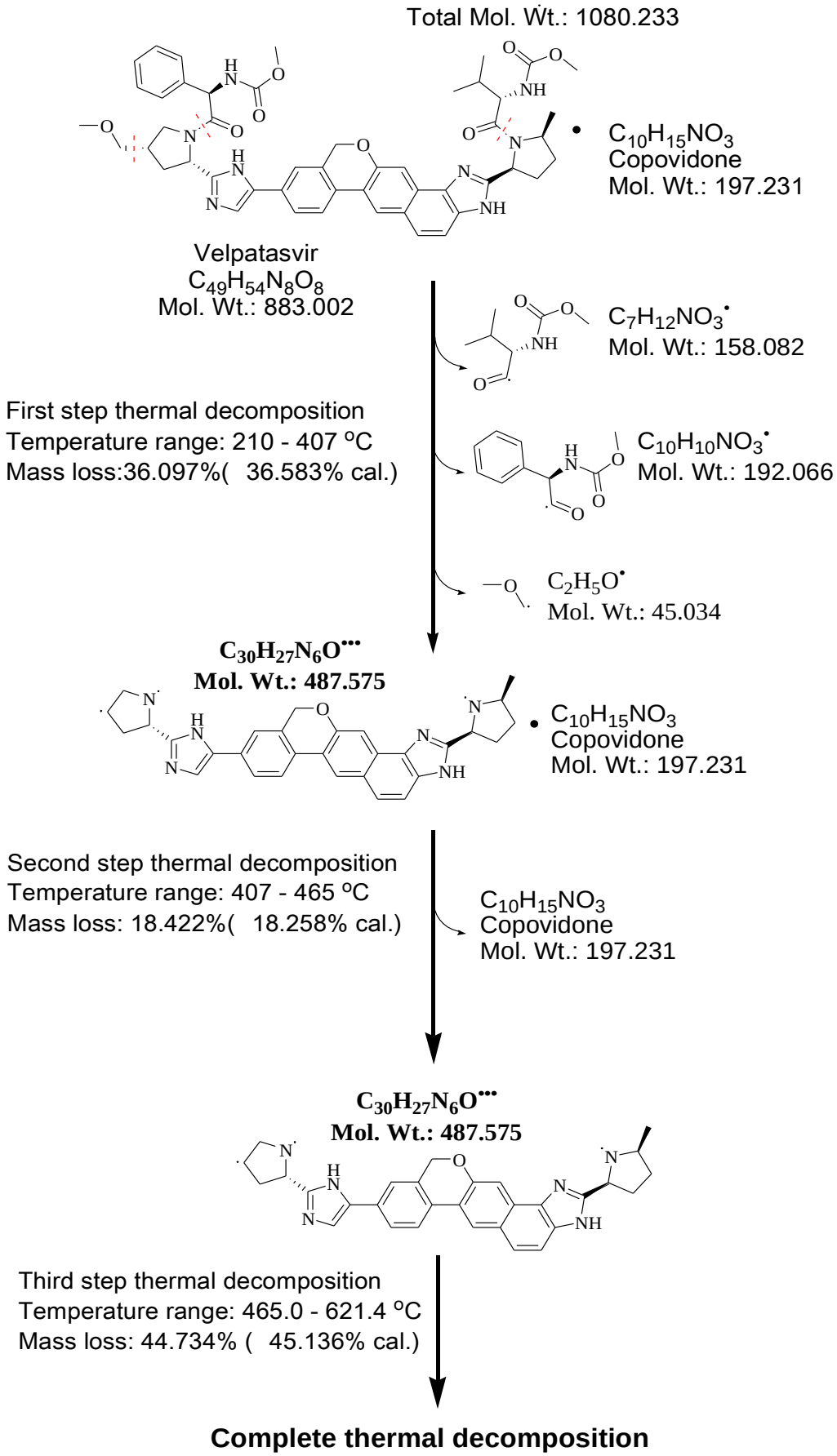


Figure 1. TG/DTG curves of velpatasvir : copovidone (1:1) in dynamic nitrogen atmosphere (40 mL min^{-1}) and heating rate 10 ºC min^{-1}



Scheme 1. Suggested thermal decomposition of velpatasvir: copovidone (1:1)

Combining equations (1) and (2) gives the following relation:

Ln[(dα/dt) / f(α)] = Ln A – Ea / RT……..(3)

Where (α) is the decomposed fraction, (dα/dt) is the rate of the reaction, f(α) = is a function of the actual composition of the sample, K (sec^{-1}) is the specific rate constant, A (sec^{-1}) is the pre-exponential term or frequency factor, Ea (J mol^{-1}) is the activation energy, R is the gas constant (8.314 J $mol^{-1}K^{-1}$), T = temperature in degrees Kelvin.

Alfa (α), (the fraction reacted at a particular temperature), was calculated from the weight (mg) of the sample at temperature T (W_T), the initial weight per mg (Wi), and the final weight per mg (Wf) using the following equation (Zhang, 2013):

$\alpha = (W_i - W_T) / (W_i - W_f)$……(4)

The differential form of equation (4) gives:

$d\alpha/dt = (d\ w_t/\ dt) / (W_i - W_f)$……(5)

The function (d wt/ dt) in mg Sec^{-1} is obtained from the DTG data. Then, the rate of the reaction can be calculated directly. This value of (d w_t/ dt) obtained from equation (5) is substituted into equation (3), and finally, a plot of Ln K versus 1/T is constructed (Figure 2), from which (Ea) and (A) are calculated from the slope and intercept, respectively.

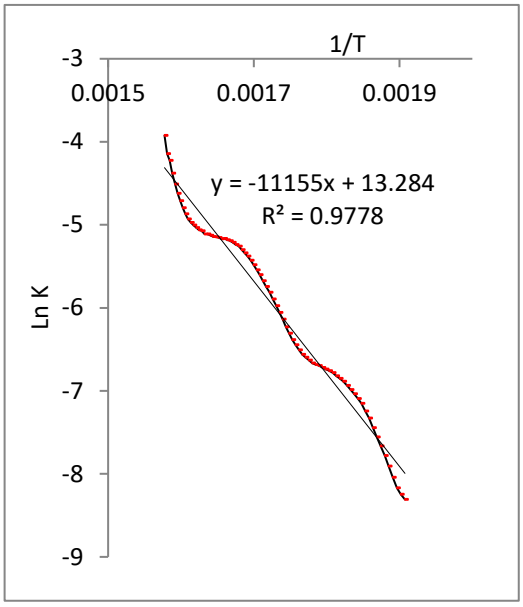


Figure 2. kinetic plot velpatasvir:copovidone (1:1) using mathematical model of Arrhenius

The calculated data evidenced a first order kinetics behavior for velpatasvir copovidone (1:1), with an Ea value of 92.777 KJ mol^{-1} and a frequency factor (A) of 5.917 x 10^5 Sec^{-1} (Table 1).

Table 1. Thermo-analytical data for velpatasvir : copovidone for the first step thermal decomposition using Arrhenius equation (AE), Coats-Redfern (CR) and Horowitz-Metzger (HM)

Kinetic Parameter	Kinetic Equation		
	Arrhenius (AE)	Horowitz Metzger(HM)	Coats- Redfern (CR)
Ea (KJ mol^{-1})	92.777	110.153	96.860
A (Sec^{-1})	$5.917x10^{+5}$	$5.932x10^{+10}$	$4.263x10^{+7}$
ΔS* (J mol^{-1} K^{-1})	-60.842	-44.364	-104.533
ΔH* (KJ mol^{-1})	87.862	105.238	91.946
ΔG* (KJ mol^{-1})	123.800	131.442	153.689
n	1	1	1
R^2	0.978	0.994	0.998

3.2.2. Horowitz-Metzger Method

Thermodynamic parameters were obtained by using the Horowitz-Metzger, which were applied to the first order kinetic process (Horowitz & Metzger, 1963). The Horowitz-Metzger equation can be represented as follows:

$$\log.[\log\frac{W_f}{W_f - W}] = \frac{\theta.E^*}{2.303RT_s^2} - \log 2.303$$

Where W_f was the mass loss at the completion of the decomposition reaction,

W was the mass loss up to temperature T,

R was the gas constant,

Ts was the DTG peak temperature, and θ = T-Ts.

A straight line was obtained by plotting log [log *Wf/(Wf-W)*] against θ, and *E** or *Ea* could be calculated from the slope (Figure 3). The calculated data also evidenced a first order kinetics behavior for velpatasvir copovidone with an (*Ea*) value of 110.153 kJ mol^{-1} and a frequency factor (A) of $5.932x10^{10}$ Sec^{-1}.

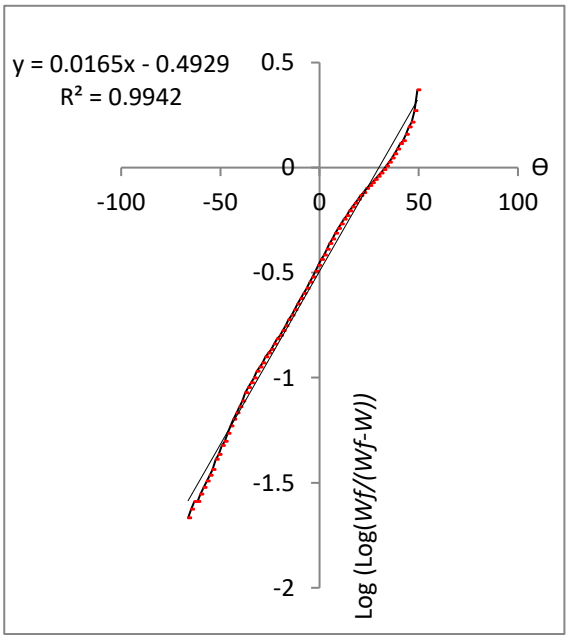


Figure 3. Kinetic plots of velpatasvir : copovidone (1:1) using mathematical model of Horowitz and Metzeger.

3.2.3. Coats-Redfern Method

This method is also applied to the first-order kinetic process (Coats & Redfern, 1964). The Coats-Redfern method equation can be represented as follows:

$$\log\left(\frac{\log\left[W_f/W_f - W\right]}{T^2}\right) = \log\left[\frac{AR}{\phi E^*}\left(1-\frac{2RT}{E^*}\right)\right] - \frac{E^*}{2.303\,RT}$$

Where Φ was the heating rate. Because 1-2RT/E* is nearly 1, plotting the left side of the equation against 1/T yields a straight line. E* (activation energy) was then calculated from the slope, and the Arrhenius constant (A) was obtained from the intercept (Figure 4). The calculated data also evidenced a first order kinetics behavior for Velpatasvir copovidone with an Ea value 96.860 KJ mol^{-1} and a frequency factor (A) of $4.263x10^{7}$ Sec^{-1}.

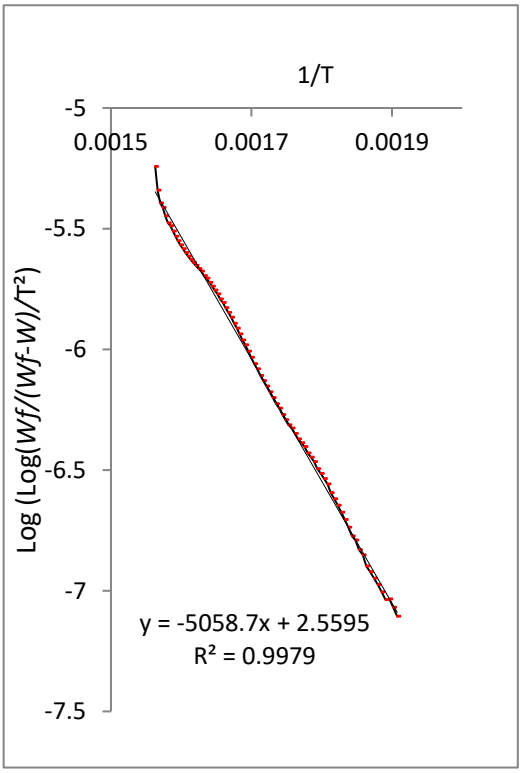


Figure 4; Kinetic plots of velpatasvir : copovidone (1:1) using mathematical model of Coats and Redfern.

The entropy ΔS*, enthalpy ΔH*, and free energy ΔG* of activation were calculated using the following equations:

$\Delta S^* = 2.303 [\log (Ah / kT)] R$

$\Delta H^* = E^* - RT$

$\Delta G^* = H^* - Ts \Delta S^*$

Where h, k, and R were the Planck constant, Boltzman constant, and gas constant, respectively.

4. Conclusions

The thermal stability of velpatasvir co-povidone using thermal technique (TGA/DTG) was studied. The kinetic studies of velpatasvir : copovidone showed a thermal behavior characteristic of first order according to Ea. The simplicity, speed, and low operational costs of thermal analysis of pharmaceuticals justify its application in quality control.

Declaration:

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