Reaction Calorimetry and Thermodynamic & Kinetic Modelling towards a faster Chemical Development

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July 2021

Abstract

The present work is in the scope of chemical process development in pharmaceutical industry. Pharmaceutical industry has been shifting to a predictive process development industry. However, there is still a lack of information on chemical systems in the early stages of the process development. Besides, some analytical tools in use do not suit the industry needs on the required information in an expedited manner. In this work, it is presented a systematic study on how to use isothermal reaction calorimetry to address kinetic and thermodynamic reaction modelling with a view to scale up. After generating simulated calorimetry and concentrated data, several modelling experiments were performed. This study demonstrates the power of reaction calorimetry on chemical process optimization and scale-up. From the present work it was possible to suggest recommendations for a preliminary methodology to use calorimetric data as a tool for kinetic and thermodynamic modelling towards a faster chemical development: (1) the use of at least 2-runs of the reaction at two different temperatures (2) how to combine calorimetry data with on-line concentration data and (3) pre-fitting of the model to the data before iterative estimation having chemical principles in mind. Overall, the objectives of the thesis were accomplished, although further studies should be conducted to widen the conclusions to more complex mechanisms and to validate the methodology on manufacturing scale. **Keywords: Kinetics, Thermodynamic, Modelling, Reaction Calorimetry**

1. Introduction

In the pharmaceutical industry, there is a consistent need to ensure that clinical supplies are manufactured and delivered in a timely manner. Delivering clinical supplies when they are needed requires the use of expedited technology. On another hand, manufacturers are constantly facing the question of the best use of the limited financial resources available. Further, process development, optimization and scale-up historically tend to be an iterative approach. This approach entails time and high costs/wastes, therefore, the industry has been shifting toward predictability at lab scale [1, 2]. All things considered, it is needed to fill the lack of information on chemical reactions, in the initial stages of the process development. This knowledge is essential to an expedited reaction optimization process to predict its scale up design.

Process development and chemical reaction optimization depend on an appropriate reaction model. For a large number of pharmaceutical reactions such model is not available or it is difficult to develop within the available time [3]. Despite, it should be possible to describe the majority of the chemical reactions using an empirical model that describes the main and side reactions, with a minimum number of reactions parameters [4, 3]. These models will allow the kinetic parameters to be estimated by fitting the model to experimental data.

There are many existing analytical techniques to follow reaction kinetics. Nevertheless, some of them are time-consuming, specially if calibration and sampling is needed (e.g. HPLC) – sometimes sampling in a form different from the original matrix. Besides, some of these techniques require a sophisticated mathematical knowledge to determine the parameters [5, 6].

Although there are many analytical tools to follow the reaction kinetics, calorimetry (measurement of the heat flow) implies that both kinetic and thermodynamics contribute to the observed signal, including phase changes and heat and mass transfer phenomena [7] (see Section 2).

For all the mentioned reasons, calorimetry has become a standard analytical tool for simultaneous kinetic and thermodynamic measurements. [5, 4, 8, 9, 10, 11, 12, 13].

In this work it is intended to formulate a method-

ology using reaction calorimetry to study reaction kinetics and thermodynamics, in the scope of chemical optimization towards its scale-up prediction in fed-batch mode.

2. Background

Reaction calorimetry requires conducting an energy balance to the semi-batch reactor – eq. (1) [14]. In a fed-batch reactor, the accumulated heat energy ($\dot{q}_{ac}$, W) is equal to the sum of all heat transfer sources: the jacket ($\dot{q}_{flow}$), the reaction ($\dot{q}_r$) and the feed ($\dot{q}_{in}$).

$$\begin{aligned}\dot{q}_{ac} &= \dot{q}_{flow} + \dot{q}_r + \dot{q}_{in} \\ &= m\,Cp\,\frac{dT_r}{dt} \\ &= U\,A\,(T_j - T_r) \\ &+ r\,V(t)\,\Delta H_r + \dot{m}\,Cp\,(T^{in} - T_r)\end{aligned} \tag{1}$$

Where, $m, Cp, T_r, U, A, T_j, r, V(t), \Delta H_r, \dot{m}, T^{in}$ are reaction mixture mass, reaction mixture heat capacity, reactor temperature, overall heat-transfer coefficient, heat-transfer area, jacket temperature, reaction rate, reactor volume, reaction enthalpy, inlet mass flow rate, inlet stream heat capacity, temperature of inlet stream, respectively.
If there is another tangible heat phenomena (as mass or heat transfer) the respective terms should be included on the balance equation. In this case, it will only be addressed homogeneous reaction systems, with negligible enthalpy of mixing.
According to Equation (1), it is easily noted that the reactor heat transfer capacity has to be characterized – through experimental determination (solvent test) or estimation by modelling to the data (without the reaction) [10] or even using empirical equations [15].

The reaction rate depends on the kinetic constant(s) linked to the mechanism at hand. The kinetic constant dependence with the temperature is expressed with Arrhenius equation – eq. (2).

$$k = k_0\,e^{-\frac{Ea}{RT}} \tag{2}$$

Where k, k_0, Ea, R, T represent kinetic constant[1], the pre-exponential factor[1], activation energy (J K^{-1}), gas constant (J mol^{-1} K^{-1}) and temperature (K), respectively.

The heat balance – Equation (1) shows mathematically the dependence of the heat signal of the reaction calorimeter with the kinetic and thermodynamic phenomena.

[1] Kinetics dependent units

As the heat flow rate during a chemical reaction is proportional to the rate of conversion, calorimetry represents a differential kinetic analysis method (eq. (3)) [8]:

$$\dot{q}_r(t) \propto r(t)V \tag{3}$$

This relation implies that subtle changes in concentration profiles are magnified in heat flow measurements.
In contrast with calorimetry, other analytical techniques applied in this context, such as concentration measurements, online measurement of reaction spectra can be compared to an integral kinetic analysis methods: the signal/measurements (s_i) is proportional to the concentration profiles ($C_i(t)$) in mol L^{-1} – eq. (4)).

$$s_i(t) \propto C_i(t) \tag{4}$$

This is why it has been defended that combinations of both calorimetry and an integral kinetic analysis techniques lead to a significant improvement on the kinetic analysis [8, 5, 4, 16, 3, 14, 17].

On another hand, pharmaceutical reactions are often followed by significant heat release, therefore they must be truly understood to be properly managed on a factory scale, as thermal instability and explosive behaviour can be extremely destructive and costly events [18]. Reaction calorimetry can help to predict the likely behaviour of chemicals when reactions, transport and storage are concerned [6].
All things considered, it is worth to include reaction calorimetry on the chemical development in pharmaceuticals, to expedite this process. The issue to be regarded is how should it be established. This work is addressing this matter by developing a systematic study of the modelling experiments.

3. Methodology

The systematic study developed during this work was based on modelling experiments based on generated data experiments. In these section the data generator will be described, followed by the chemical reaction parameters used and the experimental conditions simulated. Afterwards, the model will be briefly described.

3.1. Data Generator

The data generator is presented in this section, followed by the experiments conditions. The referred data generator was developed using Microsoft® Office Excel ® and it was applied to generate concentration and heat flow data profiles.

The system simulated in this study comprises a fed-batch, lab-scale reaction calorimeter, with volume V, where an homogeneous reaction is con-

ducted, in isothermal mode. The reactant A is fed to the reactor, during a determined time (*feed time*), starting at the moment labeled *start of feed*, see Figure 1. The reaction taking place in the

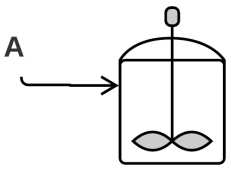

Figure 1: Schematic representation of the simulated system: semi-continuous reaction calorimeter.

calorimeter is described by a two step mechanism. The generic reaction system represents any series mechanism composed by two steps of first-order kinetics eq. (5), where the corrected kinetic constants, k_1 and k_2, are described by the Arrhenius equation rearrangement, eq. (6).

$$\mathrm{A} \xrightarrow{\mathrm{k_1}} \mathrm{B} \xrightarrow{\mathrm{k_2}} \mathrm{C} \tag{5}$$

$$k\left(T_r\right) = k\left(T_{ref}\right) \exp\left\{-\frac{E_A}{R}\left(\frac{1}{T_r} - \frac{1}{T_{ref}}\right)\right\} \tag{6}$$

Where T_r and T_{ref} represent the reactor temperature and the reference temperature respectively (K); $k\left(T_r\right)$ and $k\left(T_{ref}\right)$ are the kinetic constants correspondent to each of the temperatures (min^{-1}); R represents the gas constant (kJ mol^{-1} K^{-1}) and E_a is the activated energy, kJ mol^{-1}.

Therefore, the rate law of each step (r_1, r_2) in mol min^{-1} is defined by eqs. (7) and (8).

$$r_1(t) = -k_1\, C_A(t)\, V \tag{7}$$

$$r_2(t) = -k_2\, C_B(t)\, V \tag{8}$$

Once the mechanism was described, it was possible to write the mass balances of the three generic components – eqs. (9) to (11).

$$V\frac{dC_A(t)}{dt} = C_A Q_v - r_1(t) \tag{9}$$

$$V\frac{dC_B(t)}{dt} = r_1(t) - r_2(t) \tag{10}$$

$$V\frac{dC_C(t)}{dt} = r_2(t) \tag{11}$$

Where V is the solution volume (mL), C_A, C_B, C_C are A, B, and C molar concentrations (mol mL^{-1}) and Qv is the feed flow-rate (mL min^{-1}). The mass balance equations allow the generation of the concentration profiles with time. On another hand, the heat released (positive) or consumed (negative) by the reaction ($\dot{q}_r$) can be calculated by the eq. (12).

$$\begin{aligned}\dot{q} = \dot{q}_r &= -\sum(r_i V \Delta H_{ri}) \\ &= -(r_1 V \Delta H_{r1} + r_2 V \Delta H_{r2}).\end{aligned} \tag{12}$$

Note that the heat flow rate $\dot{q}$ (W) is equal to the reaction heat ($\dot{q}_r$, (W). To simplify the heat balance, the inlet stream was considered to be at the same temperature than the solution ($\dot{q}_{in}$ = 0). Additionally, in these chemical system there is no phase change or tangible mixing phenomena. Also, this generator does not include stirring heat ($\dot{q}_{stirrer}$), dissipated heat ($\dot{q}_{loss}$) or the heat transferred by the calorimeter jacket ($\dot{q}_{flow}$). The heat associated to these calorimeter inner components was considered to be negligible.

The differential equations were solved numerically, using the Euler method.

Once the data was generated through the balance equations, *MS* Excel® *random* function was used in order to add noise to the generated data, replicating the noise associated to the lab equipment measuring sensors/scales. For that, the random generated numbers uniformly distributed between 0 and 1 were transformed into a complex normal distribution $f(\mu, \sigma)$ with mean $\mu = 0$ and variance $\sigma^2 = 1$, by applying the following equation system, eq. (13).

$$\begin{aligned} z_1 &= \sqrt{-2\ln x_1}\cos\left(2\pi x_2\right) \\ z_2 &= \sqrt{-2\ln x_1}\sin\left(2\pi x_2\right) \end{aligned} \tag{13}$$

The result of this transformation represented by z_1 and z_2 was added to the data.

3.2. Reaction Parameters

Since the data generator math fundamentals are already described, the parameters chosen for the generic reaction may be presented. Table 1 summarizes the kinetic and thermodynamic parameters of the reaction (eq. (5)).

Table 1: Kinetic and thermodynamic parameters of each step of the reaction system.

Reaction Step i	k_i (T_{ref} = 313.15 K) min^{-1}	Ea_i kJ mol^{-1}	ΔH_{ri} kJ mol^{-1}
1	0.2	80	-120
2	0.4	80	60

The reaction starts with a slow exothermic step, followed by a faster endothermic step. The reader may notice that the kinetic constants have the same order of magnitude, although step 2 is two times faster than step one ($\frac{k_2}{k_1} = 2$). On another hand, both steps have the same dependence of the temperature, expressed by identical Ea value.

3.3. Virtual experiments

Based on the Equation (5) reaction, several experiments were generated, for instance, by changing T_r. Further experimental conditions were maintained and they are described in Table 2.

Table 2: Experiments description: common condition parameters.

Parameter	Unit	Value
V_0	mL	400
Q_v	mL min^{-1}	10
C_A^{in}	M	1
Feed time	min	2
Start of feed	min	1

4. Modelling

Two experiments were used for the systematic study, at 25 ℃ and 55 ℃. The modelling experiments were performed using DynoChem. The program model uses the same kinetic, thermodynamic and math fundamentals. This model comprises *Rosenbrock* integration solver and a *Levenberg Marquardt* fitting solver.

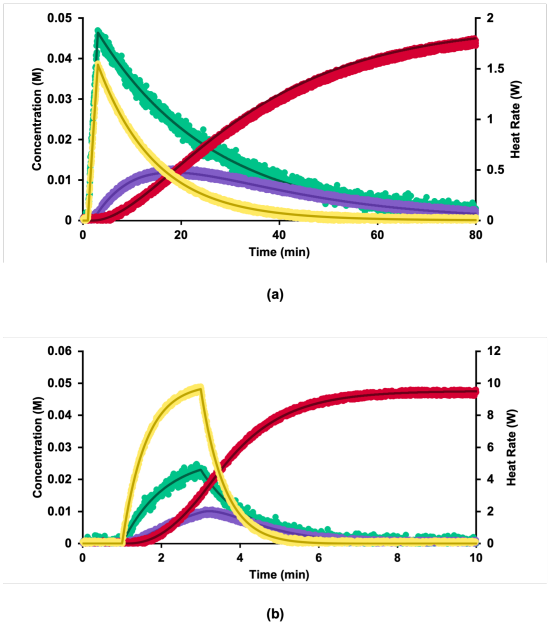

Figure 2: Model prediction (line) against the experimental data (points), stemming from 10% deviated initial iteration values using calorimetry data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃

5. Results & discussion

The systematic study is comprised by several modelling experiments using calorimetry data only and alternatively using calorimetry data combined with concentration data. Both approaches were tested stemming from different initial iteration numbers. The systematization of the initial iteration values allows the direct comparison of the different results and the analysis of the working range of the model. The initial iteration values tested are presented in Table 3 against the reference numbers – the parameters used on the simulation.

The results are presented following Table 3 sequential alignment, increasing the distance of the iteration initial value to the reference: simulating decreasingly foreknowledge of the reaction.

For all the modelling experiments the fit was performed 2 times in order to avoid misleading results resulting from local minimums.

Stemming from initial iteration values (I) – 10% of deviation – calorimetry data was used to fit the model. Followed by the same modelling experiment yet using combined data (A concentration + heat rate). Both results are summarized in Table 4. Figure 2 illustrates the heat rate fitting results, where it can be verified the model representing the experimental data. Since the results were similar, the outcome of the second experiment is not shown. In fact, according to Table 4, using both approaches model it was possible to estimate the kinetic and thermodynamic parameters – maximum error of 5.5% using simulated calorimetry data and 3.7% using the combined approach. Nevertheless, it is worth noting that with the addition of a concentration profile, the accuracy of the results increased slightly (Table 4).

The results using calorimetry data stemming from initial iteration values 50% below the reference values (II) are presented in Figure 3. According to the Figure 3, the model heat profile is accurate, although it indicates that such information is not sufficient to estimate the concentration profiles. The modelling outcome while using both concentration and heat rate data is similar to Figure 2, therefore it is not presented in this document. Table 5 summarizes the analytical results of the calorimetric and combined approach. Stemming from 50% deviated values, the concentration profile was revealed to be significant information for the kinetic and thermodynamic parameters estimation. In fact, the addition of one concentration profile decreases the maximum error associated to the parameters from 105% to 4%. In due course, the same modelling experiments were performed from initial iteration numbers one order of magnitude below the reference parameters (initial iteration number set III). According to Figure 4, heat rate profile does not comprise sufficient information for the model to converge accurately. Although there is no room for improvement in the fit of the heat data, the concentration profiles show this results are not reliable. The reaction calorimetry data does not allow the correct differentiation of the first and second step kinetics. The addition of the concentration profile does not solved this limitation. In fact the program was not able to converge when using calorimetric and concentration data to the param-

Table 3: Systematic study arrangement: reference kinetic and thermodynamic values against the initial iteration values tested and corresponding deviation.

Parameter	Reference Value	Initial Iteration Number			
		I	II	III	IV
k_1 (min^{-1})	0.2	0.22	0.1	0.02	0.01
k_2 (min^{-1})	0.4	0.44	0.3	0.04	0.01
Ea_1 (kJ mol^{-1})	80	72	40	8	60
Ea_1 (kJ mol^{-1})	80	72	40	8	60
ΔH_{r1} (kJ mol^{-1})	-120	-132	-60	-12	-120
ΔH_{r2} (kJ mol^{-1})	60	66	30	-12	-120
Deviation		10%	50%	90%	-

Table 4: Analytical results of the systematic study using calorimetry data and the combined approach ($\sigma = 0.02$): stemming from 10% deviated initial iterative numbers (I)

Parameter	Calorimetry		Combined	
	Result	Error (%)	Result	Error (%)
k_1 (min^{-1})	0.195	2.6	0.202	1.1
k_2 (min^{-1})	0.400	0.1	0.400	0.1
Ea_1 (kJ mol^{-1})	81.6	2.0	81.2	1.5
Ea_2 (kJ mol^{-1})	81.5	1.9	79.0	1.3
ΔH_{r1} (kJ mol^{-1})	-123.2	2.7	-117.4	2.2
ΔH_{r2}(kJ mol^{-1})	63.3	5.5	57.8	3.7

Table 5: Analytical results of the systematic study using calorimetry data and the combined approach ($\sigma = 0.02$): stemming from 50% deviated initial iterative numbers (II)

Parameter	Calorimetry		Combined	
	Result	Error (%)	Result	Error (%)
k_1 (min^{-1})	0.401	100.5	0.202	1.1
k_2 (min^{-1})	3.72E-4	99.9	0.400	0.2
Ea_1 (kJ mol^{-1})	81.7	2.1	81.2	0.1
Ea_2 (kJ mol^{-1})	81.9	2.1	78.9	1.3
ΔH_{r1} (kJ mol^{-1})	-59.9	50.0	-117.4	2.2
ΔH_{r2}(kJ mol^{-1})	-3.0	105.0	57.8	3.7

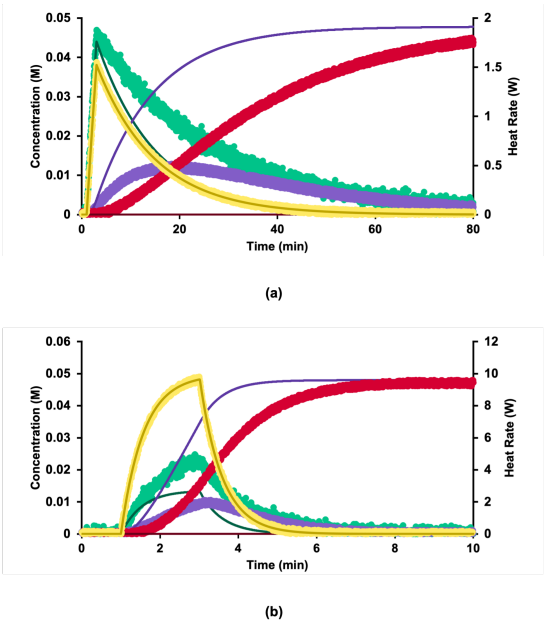

Figure 3: Model prediction (line) against the experimental data (points), stemming from 50% deviated initial iteration values using calorimetry data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃.

eters estimation. Thus, such results are only presented in the extended version of the thesis. These initial values are not plausible, showing the fitting stage of the process development requires experience and chemical knowledge to obtain reliable results.

Afterwards, generic initial values were tested (V), such results are presented in Figures 5 and 6 while using calorimetry data or combined data, respectively. These experiments were performed to reproduce the scenario where there is no foreknowledge on the reaction kinetics or its energy production/consumption. The corresponding analytical results are presented in Table 6. Overall, these results show no accuracy on the kinetic and thermodynamic parameters. The fit of the model to the heat data (Figure 5) can not assure the correct determination of the parameters (accuracy error up to 300%). In fact, the parameters which have minor error values associated are calculated from closer initial iterative values (Ea_i and ΔH_{r1}), and that is consequence of a coincidence. When A concentration is added to the fitting window, it produces a slight improvement on the first step corresponding parameters determination, as expected. Nevertheless, this addition does not solve the lack of information on the second step. Although, this is not a recommended practice, sometimes it is applied. This study shows that reagent concentration and heat profiles of two experiments at two different temperatures do not comprise sufficient information for modelling from generic values.

Overall, the results prove that calorimetry is a

Table 6: Analytical results of the systematic study using calorimetry data and the combined approach ($\sigma = 0.02$): stemming from generic initial iterative numbers (IV)

Parameter	Calorimetry		Combined	
	Result	Error (%)	Result	Error (%)
k_1 (min^{-1})	0.408	103.7	0.231	15.5
k_2 (min^{-1})	3.06E-5	100.0	0	100.0
Ea_1 (kJ mol^{-1})	82	3.0	81.7	2.1
Ea_2 (kJ mol^{-1})	60	25.0	60	25.0
ΔH_{r1} (kJ mol^{-1})	-60	50.2	-70	41.1
ΔH_{r2}(kJ mol^{-1})	-120	300.0	-120	300.0

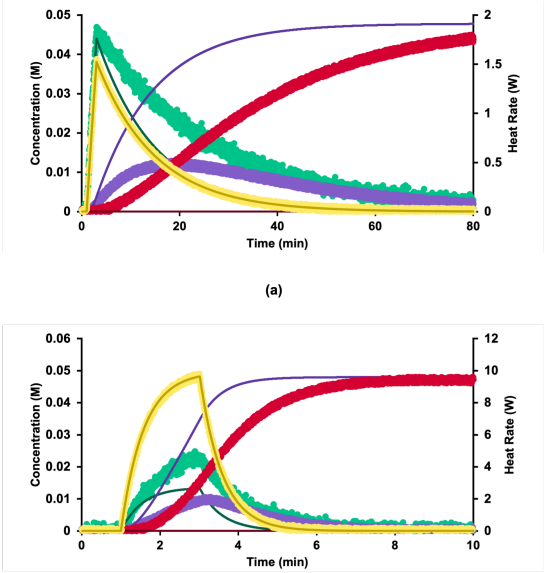

Figure 4: Model prediction (line) against the experimental data (points), stemming from 90% deviated initial iteration values using calorimetry data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃

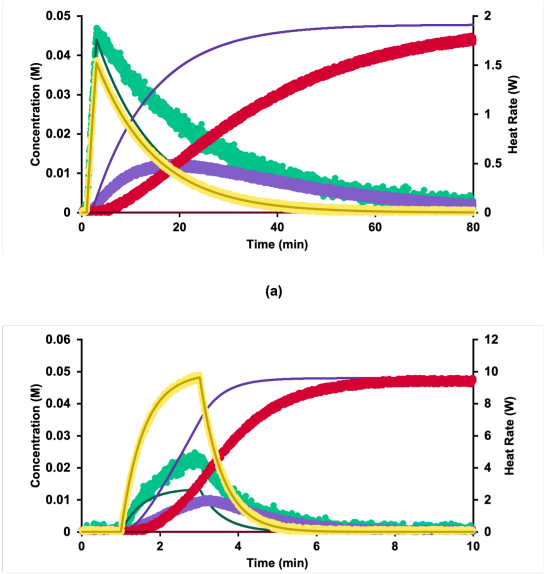

Figure 5: Model prediction (line) against the experimental data (points), stemming from generic initial iteration values using calorimetry data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃

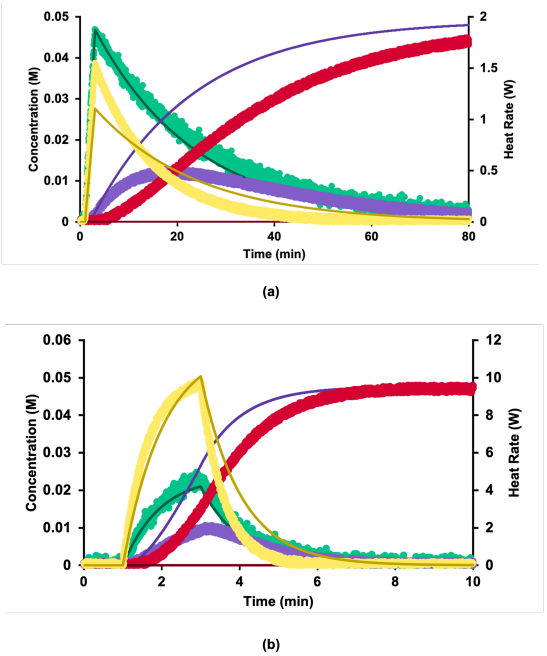

Figure 6: Model prediction (line) against the experimental data (points), stemming from generic initial iteration values using combined data at (a) 25 ℃ (b) 55 ℃

powerful tool for kinetic and thermodynamic modelling, although this modelling experiments should be conducted prudently. The chemical behaviour of the species at hand should always be considered and pre-fitting of the data is recommended.

These experiments also revealed the importance of on-line concentration data on the parameters estimation, specially when the foreknowledge of the reaction is limited. In order to understand if the on-line tools ensure advantages to the kinetic and thermodynamic modelling, the same experiments were carried out yet simulating discrete sampling instead of full progress concentration profiles: 6 concentration points instead of 3201 (at 25 ℃) and 4 points instead of 5455 (55 ℃). The off-line simulated samples were chosen in order to cover the different phases of the reaction: the initial point before the addition, after the addition and in the stationary phase.

Table 7: Analytical results of the systematic study using the combined approach ($\sigma = 0.02$): discrete off-line samples vs on-line continuous concentration profiles, stemming from 10% deviated initial iterative numbers (I).

Parameter	Off-line		On-line	
	Result	Error (%)	Result	Error (%)
k_1 (min^{-1})	0.228	14.0	0.202	1.1
k_2 (min^{-1})	0.443	10.7	0.400	0.1
Ea_1 (kJ mol^{-1})	88.3	10.4	81.2	1.5
Ea_2 (kJ mol^{-1})	89.3	11.6	79.0	1.3
ΔH_{r1} (kJ mol^{-1})	-88.8	26.0	-117.4	2.2
ΔH_{r2}(kJ mol^{-1})	28.3	52.9	57.8	3.7

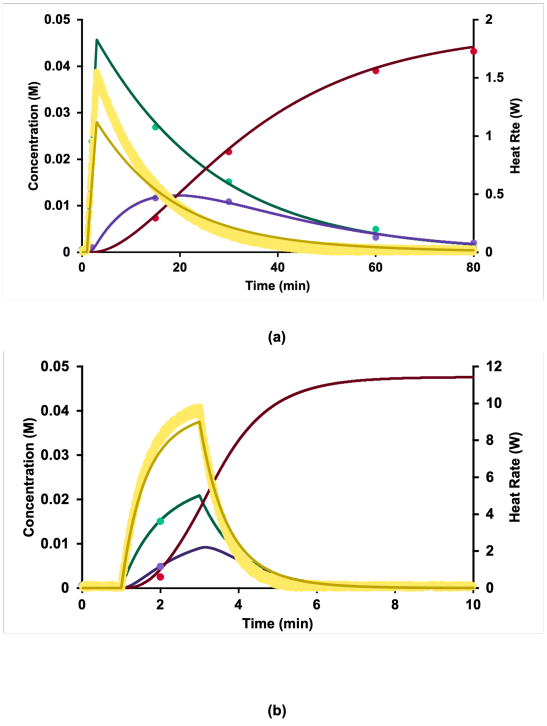

Figure 7: Model prediction (line) against the experimental data (points), stemming from 10% deviated initial iteration values using calorimetry data combined with discrete concentration data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃

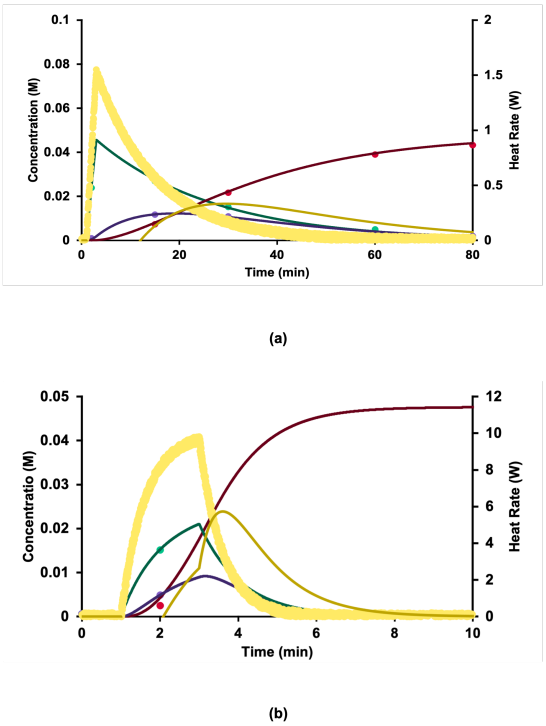

Figure 8: Model prediction (line) against the experimental data (points), stemming from generic initial iteration values using calorimetry data combined with discrete concentration data ($\sigma = 0.02$) at (a) 25 ℃ (b) 55 ℃

The modelling experiments using discrete concentration points and stemming from 10% deviated initial values (I) are presented in Figure 7. The corresponding analytical results are presented in Table 7. According to fig. 7 it is possible to verify the fit of model to the calorimetry data is not 100% accurate, although the fit to the concentration seems right. Table 7 presents the previous simulation analytical results and their respective accuracy error values, against the previous corresponding analytical results using the continuous concentration profiles. Note the previous study has taken into account only one concentration profile (reagent A), in opposition to this one with concentration sampling of three different species: reagent A, intermediate B and product C. Even though the three species were taken into the simulation, the results are more accurate while using only A concentration complete profile: 14.6 in opposition to 1.1% (k_1), 10.7 in opposition to 0.1% (k_2), 10.4 in opposition to 1. 5% (Ea_1), 11.6 in opposition to 1.3% (Ea_2), 26.0 in opposition to 2.2% (ΔH_{r1}) and 52.9 in opposition to 3.7% (ΔH_{r2}). As expected, the use of continuous on-line concentration data implies significant improvement on the accuracy of the results, over discrete sampling. This type of data improves not only the accuracy of the results, as it would save time on the parameters determination process: at the experimental stage and at the modelling stage. Nevertheless, off-line limited sampling methods are currently in use, for instance off-line HPLC (*vide* Section 1)

Afterwards, the generic initial iteration values were tested IV (Table 3). Figure 8 represent the visual outcome of the simulation, while Table 8 presents the results from discrete against continuous concentration data.

Table 8: Analytical results of double experiment study: stemming from generic initial iterative numbers, using calorimetry data with or without concentration data with noise associated ($\sigma = 0.02$).

Parameter	Off-line		On-line	
	Result	Error (%)	Result	Error (%)
k_1 (min^{-1})	0.235	17.6	0.231	15.5
k_2 (min^{-1})	0.459	14.8	0	100.0
Ea_1 (kJ mol^{-1})	82	9.4	81.7	2.1
Ea_2 (kJ mol^{-1})	88.6	10.7	60.0	25.0
ΔH_{r1} (kJ mol^{-1})	71.2	159.4	-70.6	41.1
ΔH_{r2}(kJ mol^{-1})	-107.3	278.9	-120.0	299.9

Stemming from generic values, the difference between the accuracy error is smaller, since the results using continuous profiles were already not satisfactory (error up to 300%). The addition of data about B and C has favored the estimation of the second step kinetic parameters with reasonable margin (error up to 18%). Regarding the thermodynamic parameters, the accuracy is still not acceptable (error up to 279%). These results sustain

the previous conclusion: the data should be analysed before modelling. Nevertheless, this estimation becomes harder with less data.

These brief study comparing discrete with continuous concentration data combined with reaction calorimetry shows the improvement on the results, when using for instance spectroscopic probes over discontinuous sampling methods. Even though these study compares 1 concentration profile with 3 sample sets, the results are leaning on the probes over the classical methods. In fact the on-line technique is more expedite and allows one to follow the reaction in real time and without sampling. Additionally, when the modelling experiment has more points as in this case, the experimental noise possibly becomes more insignificant. However, it should be taken into account that not all species are identifiable through spectroscopic probes and it is different from probe to probe depending on the radiation detected, which is why only one concentration profile was used in the previous study. On another hand, it would be possible to increase the number of samples taken during the reaction. In fact, in the future, it would be interesting to test this approach with different sample quantities to find the minimum samples required according to different initial iteration numbers. However, one should bare in mind HPLC sampling and data treatment are more laborious, even if it is installed on-line.

6. Conclusions

This work was based on simulated data used to perform different modelling experiments in order to study how to implement reaction calorimetry in the chemical reaction optimization process. The study was limited to a consecutive 2-step reaction. Two simulated isothermal reaction calorimetry experiments were used to estimate k_i Ea_i and ΔH_{ri}. The modelling experiments comprised heat rate data only, heat rate combined with progress concentration profile and heat rate combined with discrete sampling. This study supports a scientific base in which the final methodology could be built and possibly extended to different reactions.

To begin with, the modelling experiments even if they are done in a chemical-specific programs should be run with caution, having chemical principles in mind. Pre-fitting the data is highly recommended instead of the iterative estimation of the kinetic and thermodynamic parameters. To that end a molecular modelling tool could be combined[19]. These recommendations for the modelling stage should avoid misleading, non-reliable results from math optimization lacking chemical validity.

This study conclusion corroborate the previous ones (see Section 1): the concentration data is important for a faster and more accurate parameter determination, therefore, chemical development. In fact, the calorimetry data has the limitation of not differentiating the heat sources. To address this limitation, concentration data should be combined. On another hand, the concentration based measurements do not give information on the energy associated to the chemical phenomena. This information is crucial for safe and optimal scale-up, as explained in Section 1.

Regarding the comparison study between the discrete samples (simulating for instance off-line HPLC samples, widely used in Pharmaceutical Industry) and progress based measurements, for a more descriptive knowledge and faster development the on-line are better suited analytical techniques. For that reason, they are already being used for kinetic modelling, as described in Section 1.

This approach was revealed to be efficient to study the methodology without experimentation. Therefore, it would also be interesting to extend this study to different 2-step reactions with different kinetic and thermodynamic parameters. For instance, to simulate different $\frac{k_1}{k_2}$ and assess if this relation as an impact on the experiments that should be carried out to accomplish an accurate parameter estimation. Likewise, different combinations (order and magnitude) of ΔH_{ri} could be assessed. The studied reaction has a simple mechanism. It would be interesting to address different, gradually more complex mechanisms. Probably, with increasingly complex systems, increasingly experimentation and/or data would be needed.

The generator built during this work would allow all these possibilities by simply changing the kinetic rate law, for instance, adding more steps involved on the kinetics or changing to a parallel mechanisms, among others. Furthermore, it can be also added mixing phenomena to the heat balance to simulate more complex mixtures.

The methodology of safe and optimal scale up based on the reaction kinetics and thermodynamics should include the reactor heat transfer characterization and its scale up prediction, as demonstrated in the extended version.

Overall, the aims of the thesis were achieved: some recommendations for the methodology were extracted from this study, contributing to an predictive chemical reaction development. Nevertheless, more studies should be conducted to widen the conclusions to more complex cases.

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