Mechanistic Modelling of Product Degradation

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Abstract

Physical and chemical stability of new pharmaceutical products represent two crucial factors for the pharmaceutical industry. Manufacturers spend millions of dollars in stability programs every year to study the stability of new products. If these formulations are considered unstable under regulators guidelines, a new product needs to be designed and all of the approval process needs to be done once more, thus increasing costs.

A predictive model was developed in the gPROMS ModelBuilder platform. By analyzing experiments from accelerated conditions, the model outputs a likely shelf-life for the studied drug. The model was validated with industry data and by implementing uncertainty and sensitivity analysis on the results, shelf-life was estimated.

An additional model that predicts degradation of pharmaceutical products in its initial packaging (HDPE bottles) and in the presence of desiccants (silica gel) was developed. It was possible to conclude that uncertainty in external parameters (temperature and relative humidity) and kinetic parameters (Ea, A and B) have a great impact in product's shelf-life and that packaging provides additional protection from moisture, thus increasing shelf-life. The addition of chemical species to parenteral solutions might induce precipitation phenomena given the low solubility of the formed species. In the second part of this work, a mathematical model was developed in gPROMS ModelBuilder to calculate species concentration and precipitated species in a parenteral solution. It was possible to note that iron(III) precipitation starts at pH 2.5 for 1mM concentration and that citrate is a good chelator for this system when a 0.448M concentration is used. Although, when uncertainty of model inputs is considered (metal concentration), the previous citrate concentration is no longer effective. A concentration of 0.6M guarantees that all iron remains dissolved.

Keywords: Drug stability, gPROMS, modelling, parenteral solutions

1. Background

1.1. Solid Dosage formulations

Stability is a critical quality attribute of pharmaceutical products; therefore, stability testing plays a crucial role in the drug development process (Capen et al. 2012). The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf-life for the drug product and recommended storage conditions (ICH 2003). Therefore, it encompasses all the phases of the drug development process. A testing program for stability samples requires a tremendous amount of resources and expertise. However, it is important to note that these studies support decision-making activities of management personnel and may represent the difference between profit or loss for pharmaceutical manufacturers.

Drug product shelf-life is determined based on the time a product remains within specifications agreed upon with regulatory agencies (Waterman 2010). These specifications can be divided into two dimensions: physical stability and chemical stability. In the latter, one must assure that the drug product, in its packaging, still has the proper potency (expressed as m/m % of the API, typically no less than 95% of its initial content (Waterman & Adami 2005); On the other hand, degradants have specification limits agreed upon with regulatory agencies (ICH and FDA) due to their toxicity to humans or the uncertainty of their effects in the human body.

Hydrolytic reactions are amongst the most common processes for drug degradation (Waterman & Adami 2005). In addition to rate dependencies on temperature and moisture, hydrolysis rates can depend on the concentration of the catalytic species, usually acids or bases. With many hydrolytic reactions, such as those involving esters, reactions are reversible, making degradation products reform the drug. Under these conditions, it may be necessary to use a more complex kinetic model. Another type of reaction common in drug degradation are oxidation reactions. Oxidative degradation of pharmaceuticals can be divided in two types: 1) reactions with molecular oxygen; 2) reaction with other oxidizing agents present in the formulation. Shelf-life of oxidizable drugs can be extended by the use of antioxidants. Nonetheless, since many antioxidants are themselves consumed as they act to stabilize the drug, the shelf-life of the drug will depend on the time before the antioxidant is depleted. Another common process in which drugs
may be degraded is through reactions with excipients. Reactivity of drugs with excipients often involve reaction of nucleophilic drugs (amines, sulfides) with electrophilic excipients (e.g. esters, carboxilic acids). Assuming the reactive excipient is present in excess, many of the reactions with drugs will depend linearly on excipient concentration. Additionally, excipient impurities and degradants can react either directly with drugs or act as catalysts for other drug degradation processes e.g. hydrolysis or oxidation (Huynh-Ba 2009). This problem is very serious since excipient impurity level may vary from supplier to supplier. Light exposure can also induce chemical degradation in susceptible molecules. Although a discussion of the various mechanisms involved in photochemical reactions is beyond the scope of this work, such reactions can be divided in oxygen dependent processes (photo-oxidations) or oxygen independent (dehydrogenations or dimerizations) (Waterman et al. 2014).

Sometimes, a drug product shelf-life may be limited due to physical changes rather than in chemical changes. It becomes important when the bioavailability of the API in the drug is altered and therefore, a decrease in drug performance is observed. For solid drugs this can be seen as a decrease in the API’s dissolution and absorption in the human tract. Solid dosage forms possess quite often disintegrants. These agents are responsible for breaking the pill apart in the stomach due to a rapid expansion when in contact with water. Since solid dosage forms are often manufactured with low percentages of water, the pills when in contact with a humid environment will pick up moisture from the air and the disintegrant might break the pill when it is stored. Another possible outcome is that the slow adsorption of moisture throughout shelf life may cause a slow expansion of the disintegrant and when the patient uses it, it will not have the ability to disintegrate in the stomach, compromising the performance of the drug.

Ken Waterman has developed the Accelerated Stability Assessment program or ASAP. It consists of four elements: 1) the concept of isoconversion to compensate for the complexity of solid-state-kinetics; 2) a moisture corrected Arrhenius equation that explicitly takes into account the effects of RH on reaction rates in solid state (Equation 1); 3) a statistical analysis to both provide reasonable estimation of parameters and determine uncertainty for the extrapolated shelf-lives; 4) Combining the effect of RH on stability with

Equation 1: Humidity corrected Arrhenius equation;

$$k = A \cdot e^{\frac{-E_a}{R \cdot T} + B(RH)}$$

$$\ln(k) = \ln(A) - \frac{E_a}{R \cdot T} + B(RH)$$

Plastic containers, such as high-density polyethylene (HDPE), polypropylene (PP), and polyethylene terephthalate (PET) bottles are widely used by the pharmaceutical industry for their products. One flaw of these containers is that they are permeable to moisture vapour. Although these permeability rates may be low, the overall sorption of moisture into these containers may lead to chemical or physical instability as discussed before. Conversely, loss of moisture in liquid formulations may also lead to losses in drug performance. Therefore, it is of high importance to characterize and quantify moisture permeability of pharmaceutical containers (Chen & Li 2008). To do so, investigators measure the water vapour transmission rate (WVTR). This process consists of measuring the weight of sealed plastic bottles filled with some kind of desiccant (anhydrous calcium chloride or silica gel) that were equilibrated for a known low relative humidity. After that, they are exposed to high RH’s for a fixed time period in specific RH controlled ovens. The weight of the bottles is measured again and the weight gain during this period is the WVTR (Huynh-Ba 2009).

1.2. Parenteral solutions

A parenteral solution (PS) is a medicine that is administered directly in the patient blood stream. To develop a parenteral product, the formulator must consider challenges such as drug solubility, product stability, drug delivery and manufacturability. Clearly, a parenteral product should be formulated with a pH close to physiological, unless stability or solubility considerations override this. Often, the pH selected for the product is a compromise between the pH of maximum stability, solubility and physiological acceptability. With that in mind, many products are formulated at slightly acidic pH because of solubility and stability considerations, and the vast majority of licensed products have a pH between 3 and 9.

In liquid dosage forms, the physical stability may also be affected by environmental conditions that can cause precipitation of the API or
other components of the formulation. This may have an impact on the bioavailability of the drug and overall performance (Gibson 2005). Precipitation may occur due to sudden shifts in the solution’s pH or to an increase in the API’s particle size due to agglutination with other molecules. Shifts in pH happen when a chemical reaction between the components of the drug generate an acid or basic product, when carbon dioxide is absorbed from the environment or when the solution buffer is consumed in a side reaction (Huynh-Ba 2009).

This chemical degradation can be described by the following equations:

\[ K_{E,j} = \prod_{i=1}^{NC} C_i^{v_{ij}}, i = 1, \ldots, NC; j = 1, \ldots, NR \]

where NC is the number of chemical species taking part in NR equilibrium chemical reactions, \( v_{ij} \) the stoichiometric coefficient of species \( i \) in reaction \( j \), given concentration \( C_i \) and equilibrium constant \( K_{E,j} \).

\[ K_{A,j} = \prod_{i=1}^{NC} C_i^{\delta_{ij}}, i = 1, \ldots, NC; j = 1, \ldots, NA \]

where NC is the number of chemical species taking part in NA association reactions with chelating agents, \( \delta_{ij} \) the stoichiometric coefficient of species \( i \) in association reaction \( j \), given concentration \( C_i \) and equilibrium constant \( K_{A,j} \).

\[ K_{sp,k} = \prod_{i=1}^{NC} C_i^{\delta_{i}}, i = 1, \ldots, NC; k = 1, \ldots, NS \]

Where \( K_{sp,k} \) is the solubility product of salt \( k=1,\ldots,N, \) and \( \delta_i \) is the number of ions of species \( i \) that are generated by the dissociation of one salt molecule.

Chelation is a type of bonding between specific molecules and metal ions. Usually these ligands are organic compounds and are called chelating agents, chelators or chelants. Their action prevents the precipitation of metals at certain pH’s and their action depends also on their concentration.

In the current industrial situation, a parenteral solution as a finished product goes through three stages: manufacturing, which corresponds to the formulation of the product; biopharmaceutics, where scientists evaluate the action of the product in vivo; and stability assessment, where product is tested to stay within specifications over its shelf-life. In the latter, it is well known that the combined action of excipients, catalysts, packaging and manufacturing equipment causes to some extent the contamination of the parenteral solution with metals. At certain pH ranges these metals may precipitate, thus compromising stability of the product. Therefore, scientists elaborate on what the metals are present in solution and estimate their concentrations. They then start an intensive work of screening one chelating agent at a time at different concentrations based on initial guesses to assess the efficiency of those molecules to prevent metal precipitation. This is a process that requires a lot time and effort and may cause significant delays in the delivery of a finished product or even its failure to deliver. Moreover, this industrial problem is associated with limited analysis tools that offer limited features, lack robustness and cannot consider realistic systems (e.g. multiple metals at the same time).

2. Implementation

2.1. gPROMS

The gPROMS advanced process modelling platform is the powerful modelling tool and optimisation framework developed by Process Systems Enterprise (PSE). Advanced Process Modelling supports more efficient decisions within process innovation and design through the employment of detailed high fidelity mathematical models of process equipment and phenomena.

2.2. Performed Experiments

Experiments are used to improve the understanding of processes and create accurate models. The quality of information generated by experiments depends strongly on the experimental conditions as well as what is measured and when it is measured. In gPROMS we can consider the processing of data from experiments to estimate the values of unknown model parameters through Parameter Estimation.

When using a model, one may have experimental data acquired in laboratorial or industrial experiments. It is possible to associate this measured data with the model variables and use it as an input for parameter estimation.

2.3. Parameter estimation tool

A detailed gPROMS model is constructed from equations describing the physical and chemical phenomena that take place in the system. These
equations usually involve parameters that can be adjusted to make the model predictions match observed reality. Examples of model parameters include reaction kinetic constants, heat transfer coefficients, distillation stage efficiencies, constants within physical property correlations, and so on. The more accurate these parameters are, the closer the model response is to reality. In gPROMS, the fitting of these parameters to laboratory or industrial data is called Parameter Estimation. This estimation is based on the Maximum Likelihood formulation which in gPROMS accounts for the physical model of the process and the variance model of the measuring instruments.

3. Solid Dosage Stability

3.1. Model implementation

A lot of interest has been shown by pharmaceutical companies to have a user-friendly tool that allows the prediction of degradation on an API formulation. With this in mind, a mathematical model based on the humidity corrected Arrhenius equation referred in equation 1 was developed in gPROMS platform. To support this, a workflow is proposed to study degradation on solid formulations:

Figure 1 - Graphical User Interface (GUI): Degradation kinetics tab

Figure 2 - GUI: Experimental conditions tab;

In figure 1 the user can specify the kinetic model to be used (default zero order) and the modified Arrhenius parameters can be inserted after parameter estimation. In figure 2 the user specifies simulation time, temperature and RH to perform the shelf-life analysis while in fig.3 initial degradant percentage can be inserted. This has to do with degradant that is often found in excipients coming from the suppliers or degradant that was formed during the product formulation process. Finally in fig.4 the user specifies the maximum limit for the studied degradant.

3.2. Case Study 1

The first case study comprises a series of experimental data under accelerated conditions. This data is characterized by the % of degradant product in total API formulation over time. It was measured over 5 experimental conditions of temperature and relative humidity with a maximum specification limit of 0.8%. It is important to notice
that a degradation of 0.524% was already present in the initial measurements. After these experiments were inserted in gPROMS ModelBuilder, the parameter estimation tool predicted the following values for the kinetic parameters: $E_a=18.65$; $\ln(A)= 21.91$; $B=0.0036$.

Applying the estimated parameters to the developed model Degradation regressor and implementing the storage conditions of 298K and 60%RH (storage conditions recommended by the ICH guideline Q1A for long term stability testing allowed the estimation of a possible shelf-life for this drug. As seen in figure 6, the degradant percentage surpasses the specification limit by the day 3070, what corresponds to approximately 8.4 years. This was accomplished while using the zero-order model given the linearity of the provided data.

### 3.3. Global Systems Analysis

Nonetheless, this value is meaningless given that there were no uncertainties associated in the calculation. In a real case scenario, the temperature and RH will not be constant (external parameters) neither will the kinetic parameters ($E_a$, $\ln(A)$, $B$). At a given time point, a higher temperature and RH may cause the drug to temporary lose its crystallinity in a given point of the lattice making its molecules become more mobile. This means that less energy will be required to activate one of the chemical degradation reactions occurring in the formulation, thus decreasing $E_a$.

In order to test the relevance of these values, the global systems analysis tool was used. An uncertainty analysis was performed with a simulation time of 730 days, corresponding to two years of the shelf life. This is the typical shelf-life value for most pharmaceutical drugs. A 500 sample size was used in the uncertainty analysis. Figure 7 shows the moving average degradation % of the two sampling methods present in gPROMS Global System Analysis. It is possible to verify that a Quasi-random Sobol sampling converges faster than a pseudo-random sampling due to it’s location memory properties.

![Figure 6- Shelf life analysis with the Solid dosage model;](image1)

![Figure 7- Moving average of degradation with Sobol sampling and pseudo-random sampling;](image2)

![Figure 8- Normal distribution on temperature;](image3)

![Figure 9- Normal distribution on RH;](image4)

Figures 8 and 9 depict the design space on the two external factors for the uncertainty analysis. A normal distribution for temperature was used with an average of 298K and a standard deviation of 12K. For the RH, a normal distribution with an average of 60% and a STD of 20% was used. In this case study, Monte Carlo simulation demonstrates that there is a strong correlation between temperature and degradation rate. On the other hand, RH does not seem to be correlated with degradation since there is not a trend in the scatter of figure 9.
Another feature of gPROMS Global System Analysis is its capability of generating histograms (absolute and normalized) and a distribution statistics table. Figure allows the extraction of the percentage of samples that were already over the specification limit at the 2 year shelf life. This value was equal to 12.4%.

Another Global system uncertainty analysis was performed in two scenarios: 1) using normal distributions only on external parameters (figure 10); 2) Using normal distributions in all the parameters (figure 11). This analysis was performed over 720 days and over 100000 samples. In the first scenario, the probability of failing specification was 12.4% (as seen before) while for the second scenario the probability of failing specification limit was 35.8%. This reveals the importance that uncertainty on kinetic parameters might have in degradation models. Additionally, it is an important factor for management personnel to decide whether this is an acceptable failure rate to keep going with the degradation experiments or if it is a better move to invest in understanding more on the certain values for the kinetic parameters that are responsible for the most variability in the results. Even though the model has a good data-fit, if the uncertainty of the model parameters is not taken into account, the predicted shelf-life may not be feasible. Therefore, a statistical analysis should always be performed.

3.4. Packaging integration

As seen in figure 13 applying the same shelf-life of 8.4 years (approx.3000 days) predicted by the model degradation regressor to the packaging model, it is possible to see that degradation fails to achieve the specification limit. This means that the HDPE bottle provided some extent of protection to the drug on the inside thus increasing its shelf-life.

4. Parenteral Solution Stability

4.1. Model development
To effectively use this model, the user starts by building the flowsheet with the template model that contains the chemical equilibrium equations by drag and drop. The user then selects options such as the minimum and maximum pH for the experiment and the number of conditions. The available number for the latter parameter vary between 10 and 50, meaning that if the user chooses 50 pH conditions, gPROMS will divide pH range in 50 portions. Choosing 10 pH conditions lowers resolution of the results thus decreases running time of the model. After this step, the user proceeds to the equilibrium reactions tab where he will choose metals from the database by clicking the three dotted button in figure 15. Clicking this button pops up a new window with all the available metals from the database. After they have been selected, the metals will then appear as chosen metals and the model will automatically create new boxes for the metal molar concentration. As seen in figure 15, because only Fe³⁺ is selected, there is only one box in the metal concentration variable. Solution volume is also needed in order to close all degrees of freedom of the model. The user then proceeds to the chelating reactions tab (figure 16) where he will choose a chelating agent from the database by clicking the three dotted button on the right. This action pops up the chelating agents database. Again, this action creates new boxes in the chelating agent liquid molar concentration according to the number of chosen chelating agents. Finally, in the solubilization tab, the user will have to manually input the Log(Ksp) for the solubilization reactions occurring in the created system. Because this variable is an array of the chosen metals variable, the model will automatically create new boxes for the Log(Ksp) according to the number of chosen metals. This means that if the user had chosen iron and aluminium, he would be asked to assign two Ksp’s in this tab.

4.2. Case Study

In this simple case, citrate was chosen based on experimental testing (figure 18). Nonetheless, taking in consideration that chelating agent database is still in development, one may want to screen all the chelating agents at the same time to see which one is more effective in avoiding metal precipitation. To do so, the user may perform a GSA.
sensitivity analysis on all chelating agents available and applying the factor prioritisation methodology to decide which one is more suitable for that specific case. The sensitivity analysis will rank all the chelating agents selected and calculate which one or ones are responsible for the greatest variance in model outputs (supersaturation). In this case study, citrate was the most relevant chelating agent to be studied. Nonetheless, pricing and availability may also be a decisive factor for the choice of a certain chelating agent so one must have that in consideration. The next step was to incorporate uncertainty in the model by doing a gPROMS uncertainty analysis. Metal concentration in a batch of parenteral solution bags or vials will have an associated uncertainty that is most likely to follow a normal distribution. Assuming that the average of iron in a parenteral solution is 1mM and STD is 10% of it (0.1mM), an uncertainty analysis on 500 samples with quasi-random Sobol sampling was performed using GSA. Additionally, one can also consider a normal distribution on chelating agent concentration. Although, in an industrial situation, the standard deviation for this value is quite low given it is added in accordance with the needs of the batch. The optimized value was chosen as mean of the normal distribution and a standard deviation of 0.1% was assumed.

Now that citrate is known to be the most relevant chelating agent among others from the database, what is the minimal concentration that prevents any precipitation for an iron concentration of 1mM? A minimisation of its concentration was done using gPROMS optimisation tool. This prevents adding more quantity than the one that is really necessary to prevent any precipitation. To do so, it was asked the optimisation tool to solve the inequality $0 < \text{Supersaturation} < 1$ and also that the variable mass of metal in the solid phase must be equal to zero through all the pH range. The optimisation procedure resulted in an optimized citrate concentration of 0.4488M. Running the Parenteral Stability model again with this value on the chelating agent, resulted in figures. It possible to note that the solid species of iron hydroxide is not present in the given pH range and supersaturation peaks at 0.7 for pH 10.

<table>
<thead>
<tr>
<th>Probability of supersaturation</th>
<th>0.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supersaturation</td>
<td>0.7</td>
</tr>
<tr>
<td>Chelating agent concentration (M)</td>
<td>0.4488</td>
</tr>
</tbody>
</table>

Figure 20-GSA using citrate as chelator with a 0.6M concentration;

Citrate was then optimized to 0.6M by trial and error. An uncertainty analysis was then performed again with the same distributions on metal and chelating agent concentration. By figure 20 it is possible to note that only one sample was supersaturated giving a probability of failure of 0.2%.

4.2.1. Multiple metals

In a real industrial situation, a parenteral solution will have multiple metals dissolved at the same time. Their concentrations may vary given the different types of contamination sources. This work represents the first attempt in literature to model multiple metals speciation in a parenteral solution. It was a much more challenging concept to implement given that chelating agents will now scavenge for different metals given the reaction rates for each chelator-metal reactions. While in theory this may seem an easy concept to understand, translating it to a programmable language makes it much harder to implement. In figure 20 it possible to see supersaturation of iron and aluminium. Precipitation of iron starts at pH 4.5 while aluminium precipitation starts at pH 7.5. In the latter, supersaturation goes below 1 for pH’s above 8, interrupting precipitation and dissolving again the metal that was already in the solid phase.
4.2.2. Multiple chelating agents

Although, as shown in figures 22 and 23, when uncertainty in added to the system, results may be surprising. In this specific case it was seen that when adding a normal distribution on iron concentration having as average 1mM and as STD 0.1mM for pH's above 2.5 the parenteral solution may or may not be supersaturated depending on metal concentration. The same goes for the mass of metal in the liquid and solid phase for the given pH range.

5. Conclusions

In this work, mathematical models were developed for the stability of solid dosages and parenteral solutions. In both parts of this work, an easy to use interface in a drag and drop flowsheet with automatic reporting of results was built to give the end user a better overall experience and data interpretation. Although this kind of architecture is not relevant in the present work, it was a great challenge to make sure that the models were robust for a wide range of variable inputs.

In the Solid Dosage stability models it is known that the isoconversion approach fails for more complex reaction mechanisms due to overly simplistic models. Model drawbacks may be overcome by classifying the diverse degradation mechanisms and account them into the models, considering the molecular and reactional aspects both of APIs and excipients used. Nonetheless, it has been shown that incorporating packaging models in accelerated stability programs of solid dosage drugs is of high importance. This addition allows the understanding of the level of protection a given type of package provides to pharmaceutical drugs against relative humidity. Solid dosage stability models along with GSA capabilities allow a better understanding of degradation processes and help management personnel take more confident decisions; They also reduce experimental cost and process time given its ability to quickly analyse "what-if" scenarios.

In the Parenteral Stability model it is possible to conclude that building cases where the user can add multiple chelating agents and metals at the same time is of extreme importance. Another feature of using the Parenteral stability model along with gPROMS features is that it enables the scientist to have a broader understanding of what is happening in solution. Meaning that if the system is composed of different metals and multiple chelators are also being used, he can start by studying the system in a univariate way. Once he understands what are the main reactions for each metal and chelator, he can then proceed to a multivariate analysis, incorporating groups or even all metals in the system and build a layered knowledge of why precipitation might occur. This model empower the user to build an integrated knowledge of their systems with an easy to use interface. Moreover, this model along with gPROMS optimisation tool and GSA capabilities represents one way of submitting work to the regulatory agencies with more confidence, resulting in more approved decisions and thus reduced costs.

It was also shown the importance of including uncertainty and sensitivity analysis on drug degradation experiments. This is an implementation that was not found in literature and there is still a lot of work to be done in this field of expertise. In addition to that, this work was the first one of its kind to study multiple metal precipitation in parenteral solutions applied to pharmaceutical cases while applying statistical analysis at the same time.

For regulators, more than assuring that a pharmaceutical product is stable, one must assure that it is statistically reliable. It has been demonstrated with the present work that
incorporating different sources of uncertainty in model inputs might affect dramatically model outputs. Therefore, this work also represents one step forward in providing regulators with meaningful data to reduce risks for patients.

This work opens a new perspective in stability testing of solid dosage forms with the incorporation of packaging models and with the powerful gPROMS parameter estimation tool. Moreover, it represents pioneer work in parenteral stability modelling given the built-in databases for different metals and chelating agents.

Future work in this field may require scientists to detach from this law-approach and focus on a more mechanistic approach. This involves defining all the possible degradants that appear in a certain formulation and hypothesize about cross-reactions that might occur between all the components in a drug. In addition to that, incorporating physical degradation models is of high importance. These models account for degradation processes occurring in the solid and will improve the understanding of overall product stability.

On the other hand, in the Parenteral Stability models one might want to increase metals and chelating agents databases to have a full spectrum of options. This increase in databases would cover a more realistic situation where parenteral solutions might have different metals in different residual concentrations. One might also want to consider cross-reactions with other molecules that can also form precipitates such as phosphates or sulphates. Calcium phosphate precipitates have extensively described in literature as one of the most common precipitating molecules in parenteral nutrition and have even caused severe diseases in patients being treated. These molecules can also affect chelating associations and can form new species with chelating agents. Adding them to the database would also provide a broader understanding of real situations. In the present work, only the precipitation of insoluble salts was studied. Nonetheless as described before, parenteral solutions show other stability problems such as lipid peroxidation and globulization, vitamin degradation and amino acid interactions. These problems might be addressed in the future in a modelling perspective to manufacture products that are more stable and safer for patients.

Finally, gPROMS is a powerful tool with integrated parameter estimation tools that allows the user to easily extract and validate kinetic parameters. Moreover, the recent addition of the Global Systems Analysis opened a new window of possible work to be done.

6. References


