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PhD. Thesis Summary:

Application of mathematical modeling in the technology of biomaterials based on apatites

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1. Introduction

Precipitation processes are widely used in industry, their complete design is difficult to develop because they must be designed to meet stringent requirements for some of the product properties such as size distribution, average particle size, morphology, purity and crystallinity in the same time. All these properties are influenced by several simultaneous phenomena such as nucleation, growth, aggregation, agglomeration, fragmentation, attrition and hydrodynamic and mixing conditions during the process [1-8]. Usually, precipitation processes occur in simple reactors: continuous, discontinuous or semi-discontinuous with mixing (slow reaction) and T-shaped mixers and Y (rapid reaction) [9-13].

When switching on an industrial scale, the product properties can be modified by changing/variation of process parameters. Operating conditions to achieve desired product properties can be selected either through an approach that aims to repeat experiments or through an optimization process based on the model. Model-based design and optimization requires knowledge of the key mechanisms in the formation and crystal growth. Therefore, the aim of this thesis is to find the appropriate method for the determination of all relevant mechanisms and develop mathematical models to simulate the precipitation process of hydroxyapatite.

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is the major inorganic component of bones and teeth, being accepted as a material with various uses for medical purposes. Also it is much used as heterogeneous catalyst [15-17], catalyst support [18.19], support for drugs [20.21], broker / adsorption of ions [22.23], support fungicides [24 - 27].

The preparation method and experimental conditions strongly influence the chemical and physical properties of hydroxyapatite, which are closely related to chemical reactivity [28]. The best known method of obtaining PAH is precipitation reaction when hydroxyapatite precipitate from supersaturated solutions. The first step is to quickly form a metastable phase of amorphous calcium phosphate, which over time turns into hydroxyapatite.

Induction time and rate of transformation of amorphous calcium phosphate into hydroxyapatite is influenced by the extent of super-saturation, solution composition, ionic strength, pH, temperature and surface active substances that alter the surface tension.

In conclusion, to obtain materials with well-defined and reproducible properties, requires rigorous control and regulation of working parameters in all

stages of synthesis. This control can be achieved only under conditions which called for the predictive management process, which requires knowledge of the mathematical model.

Recent studies of the literature [29.30] show that are no data about the mathematical modeling of components in the process technology of hydroxyapatites. Also there are no data about the use of mathematical models as tools for predictive control and management of hydroxyapatites based biomaterials technology. Introducing of process computer and predictive management of the process sets the conditions for obtaining materials with well defined properties.

2. Modeling precipitation processes

Chapter 2 of the thesis presents two issues to be taken into account to obtain the mathematical model that describes the process of precipitation.

Mathematical modeling is an attempt to transfer / translate knowledge and understanding of a process in mathematical relationships which allow the description of the evolution of system properties

Development of a mathematical model for the precipitation process has as a starting point the knowledge of the physical and mathematical laws of conservation and the population balance of crystals and the material balance. These conservation laws describe the dynamic behavior of the system. To describe the dynamics of the dispersed phase (particles) is used the population balance equation and for describing the liquid phase is using a mass balance equation for the solute concentration [31]. The concept of population balance equation was introduced in chemical engineering by Randolph and Larson [32] and Humbult and Kratz [33]. Population balance equation is a differential equation with partial derivatives which takes into account the different mechanisms by which particle is formed, evolves or disappears from the system. An overview of the techniques for solving the population balance equation is given in a statement made by Ramkrishna [34.35].

Solving techniques applied can be classified into four broad categories [36]: the method of moments, where only low order moments of particle size distribution are simulated and a distribution of unknown parameters are adjusted after deducted moments [33], orthogonal collocation method, where the solution is approximated by linear combinations of the basic functions [37], finite difference methods/discretized population balance [38] and Monte Carlo simulation, in which history of individual particles is tracked [36]. Depending on the system investigated, a detailed description of solid phase precipitation process is necessary. This description includes the main phenomena, nucleation and particle growth and secondary phenomena of fragmentation and agglomeration [39]. All these phenomena are included, as long as they are considered in the model, in the population balance equation as kinetic rate expressions.

Modeling particle size distribution in crystallization processes reveal the influence of operating conditions on final product quality. Calculation of kinetic parameters by mathematical analysis of particle size distribution and correlation of experimental data represent the basis of crystallizer's correct sizing, optimization or control of precipitation-crystallization processes

3. Fundamental mechanisms during precipitation processes

In Chapter 3 are presented the main phenomena that occur during the precipitation: nucleation, particle growth, agglomeration and fragmentation, all having supersaturation as the driving force [40].

Nucleation refers to the spontaneous formation of stable molecules cluster solution and requires large supersaturations. If a solution does not contain foreign solid particles, nuclei are formed by homogeneous nucleation. Homogeneous nucleation requires high supersaturations. The presence of foreign particles facilitates heterogeneous nucleation due to surface provided on which the nucleus can join. This latter type of nucleation occurs at lower supersaturations [25]. Once the nuclei become thermodynamically stable (nuclei that exceeded the critical size), they begin to grow and become crystals with viable size. Crystal growth from solution involves two major processes:

1. mass transport from solution to crystal surface by diffusion, convection, or combination of both mechanisms;
2. incorporation in the crystalline network by integrating on the material surface, is described as a surface reaction process

Mechanisms that govern these stages are not fully understood [41.46] and the desire to explain them theoretical models have been proposed: the diffusion-reaction models and integration at the crystal surface. There have been proposed several theories of growth of the crystal by integrating at its surface: the continuous growth model, screw dislocations or model BCF (Burton-Cabrera-Frank), bi-dimensional nucleation model or birth and spread model (B & S - "birth and spread "). It is not possible to combine all of these phenomena equations derived in an overall growth rate expression because it is possible that some events take place simultaneously.

A secondary particle formation process, which can significantly increase the final size of the crystal, is agglomeration/aggregation. This phenomenon is present in systems with high levels of supersaturation, such as precipitation, and is assessed together with crystals fragmentation. These secondary processes are characterized by low speeds and as a consequence, they usually take place after the formation of particles, does not consume the molecules in solution, leaving unchanged the total mass of particles. Agglomeration is the union of individual particles by chemical forces, forming a crystalline bridge and aggregation represents the chaotic collection of particles caused by Van der Waals forces or electrostatic forces [46]. In a

supersaturated solution agglomeration is predominant, having the effect of changing particle size distribution and only if is avoided we can obtain small particles [40].

4. Population balance equation

In Chapter 4 is presented the population balance equation, a widely used tool for simulation of precipitation processes [49.34] because it incorporates all the phenomena that occur during precipitation: nucleation, growth and simultaneously agglomeration/particle fragmentation. Population balance equation is the balance of the number of crystals in a size range in time, in a batch reactor can be written as [50]:

$$\frac{\partial n(L,t)}{\partial t} + G\frac{\partial n(L,t)}{\partial L} = B - D \tag{1}$$

where G is growth rate independent of size, L is characteristic of particle size (length / diameter) and it is time. B and D terms and represents formation (birth) and disappearance (death) particles [50]. By assuming that the volume and length are related $v = L^3$, then L and L' are particle size of volume L^3 and L'^3 (L is the small particle and L' is the larger particle size) [50]. The term $k_B(L)$ is a function of particle velocity fragmentation and $g(L,L')$ is the fragment distribution is the function that contains information about the event fragments produced by fragmentation [51].

Function $g(L,L')dL$ gives the number of fragments of size between L and $L + dL$ that result from the fragmentation of particle of size L'. Population balance equation becomes:

$$\begin{aligned}
\frac{\partial n(L,t)}{\partial t} + G\frac{\partial n(L,t)}{\partial L} &= \frac{L^2}{2}\int_0^L \frac{\beta((L^3 - L'^3)^{\frac{1}{3}}, L')}{(L^3 - L'^3)^{\frac{2}{3}}} \cdot n((L^3 - L'^3)^{\frac{1}{3}}, t) \cdot n(L',t)dL' \\
&\quad - n(L,t)\int_0^\infty \beta(L,L') \cdot n(L',t)dL' \\
&\quad + \int_L^\infty g(L,L') \cdot k_B(L') \cdot n(L',t)dL' \\
&\quad - k_B(L) \cdot n(L,t)
\end{aligned} \tag{2}$$

Population balance equation can be solved exactly only in simple cases, numerical solutions are therefore necessary. Transforming the population balance equation in the moment form is the most common method to simplify the equation and at the same time to maintain the essential characteristics of the distribution of particles in solution [49]. The standard method of moments, the key is the formulation of the problem in terms of lower-order moments in closed form (this

means that only functions of moments are involved). Thus, for a homogeneous system, time is defined as:

$$\mu_j = \int_0^\infty L^j \cdot n(L,t)dL \qquad (3)$$

The first four moments are of interest because they are correlated with the number of particles ($N_t = \mu_0$), the total area of particles ($A_t = k_a \cdot \mu_2$) and total particle volume ($V_t = k_v \cdot \mu_3$) by factors of form (k_v , k_a) that depend on particle morphology. Average particle diameter $\overline{d_p}$ can be determined by these moments, using the approximation:

$$\overline{d_p} = \frac{\mu_1}{\mu_0} \qquad (4)$$

Using the method of moments, the population balance equation can be transformed into a set of ordinary differential equations that describe the changing of moment's distribution in time [33]. Solving this system of differential equations are obtained the four moments of particle size distribution at different times, of which using equation (4) is theoretically possible to extract the theoretical diameter / simulated. In this way the theoretical average diameters are obtained, which will be adjusted to experimental diameters to determine the kinetic parameters.

5. Nucleation kinetics

Precipitation from the solution includes several phenomena such as nucleation, growth, agglomeration and particle fragmentation. Particle size distribution, size and polymorphic form of the precipitated product is the result of all these phenomena. Measurement of nucleation kinetics for the precipitation at large supersaturations is virtually impossible, therefore was not achieved in this work.

6. Growth and breakage kinetics

Chapter 6 brings together information from literature about the methods of determining the kinetics of growth. The ability to determine the kinetics of growth and fragmentation is of particular importance for the modeling of precipitation. Several methods have been proposed in the literature to determine the growth rate of particle precipitation processes:

- *measurements made on individual crystals*
- *measurements made on populations of crystals (*this includes the methods of measurement based on laser diffraction, for determining particle size distribution*)*

To facilitate the measurement of growth rate different experimental techniques are used. In practice empirical expressions are used, the aim being to describe the growth rate as reasonable depending on work conditions. Those terms should include at least the driving force for crystal growth, ie, supersaturation S. Supersaturation and crystal size may be approximately constant during growth, or have significant variations. Measurement that defines the growth rate can be obtained from the crystal changes (eg increase in size or weight) or changes in solute concentration of the solution due to crystal deposit. For many reactions involving the precipitation of insoluble salts of calcium, the growth rate G is given by a kinetic equation of the form [41]:

$$G = k_1 (S-1)^{k_2} \tag{5}$$

where: k_1 is the factor (constant speed) and k_2 is order growth rate and are empirical parameters that are determined experimentally. Supersaturation S used to calculate the growth rate is defined as:

$$S = c / c_{sat} \tag{6}$$

where c and c_{sat} is the concentration and solubility of hydroxyapatite. Based on the order growth rate k_2, the probably growth mechanism can be deduced, using a synthesized data from literature [54], taking into account that several elementary processes occur simultaneously. Temperature strongly affects the crystal growth rate, and therefore will significantly affect the relative speed of diffusion and integration steps in the crystal surface. Most times the growth rate will be raised to high temperatures, as crystal size and shape will also change with temperature [53].

7. Phase transformation: amorphous calcium phosphate in hydroxyapatite

In this chapter are presented the experimental results about the influence that pH and temperature has over the transformation rate of amorphous calcium phosphate in hydroxyapatite. Experimental results obtained from the kinetic study undertaken formed the basis of mathematical modeling of the transformation in HAP [73].

Kinetics of the transformation of amorphous calcium phosphate to HAP, which can be described by a first order reaction law, is only a function of the solution pH at constant temperature. Among the methods of preparation by precipitation the most widespread can be described by the equation:

$$10\,Ca(NO_3)_2 + 6(NH_4)HPO_4 + 6NH_4OH + 2NH_3 \rightarrow$$
$$\rightarrow Ca_{10}(PO_4)_6(OH)_2 + 20NH_4NO_3 + 6H_2O \tag{7}$$
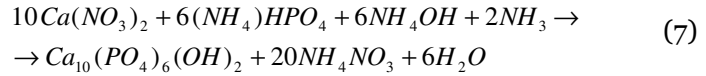
Hydroxyapatite formation process can be described as one of the following macrokinetic mechanisms:

a. mass transformation (chemical reaction - formation and growth of germs)

b. mass transfer

c. combined models (mass-transfer formation and growth of germs)

The mathematical model corresponding the macrokinetic combined model of germ formation and growth is shown by equation (8):

$$\frac{dv_{[]n}}{d\tau} = (1 - v_{[]n}) \cdot v_p \cdot \frac{dN_p}{V_{[]m} \cdot d\tau} + (1 - v_{[]n}) \cdot N_p \cdot \frac{dv_p}{V_{[]m} \cdot d\tau} \tag{8}$$

Because the process takes place at constant supersaturation, it is assumed that both germ forming and transformation – growth rate are constant. Based on these assumptions follows:

$$\eta = 1 - e^{-K_2 \cdot \tau^4} \tag{9}$$

$$\eta = 1 - e^{-K_2 \cdot \tau^2} \tag{10}$$

$$\eta = 1 - e^{-K_1 \cdot \tau} \tag{11}$$

Equations (9) (10) and (11) allow calculating the time required for the fraction $v_{[\ ]n} \equiv \eta$ of the newly formed phase (HAP) to reach a certain value (between 0 and 1). Using this equations assume experimental measurements to verify the assumed kinetic mechanism as well as the numerical values for K1, K2 and K3 of the three equations.

In all the experiments were prepared: solution of calcium nitrate with concentration 0.5 mol / l and ammonium phosphate solution with concentration 0.3 mol / l. In both solutions was added ammonia solution to adjust pH value at 8.5, 9.1, 9.7, 10.2, 11.3, 12. At set times, from the reaction mass samples were taken which were filtered, washed with distilled water and dried at a temperature of 105 °C and then was calcined for 2 hours at 1000 °C.

7.5. Experimental results

To determine the constants K1, K2 and K3, were graphically represented the three equations (9) (10) and (11) in coordinates: $-\ln(1-v_{[]_n}) = f(\tau)$. The analysis results show a very good agreement with the experimental results calculated only for equation (10), where the error for most results does not exceed 2%. From the slope were calculated numerical values of the constants K1, K2 and K3 and subsequently used in the simulation process. In order to identify the mathematical model that describes the process, we continued with the simulation of the process. In the simulation process we used the numerical values of the constants K1, K2 and K3 with the experimental values of the conversion values to calculate the necessary time to achieve a certain degree of conversion values. The analysis results show a very good agreement with the experimental results calculated with the equation (10), thus confirming the correctness of the model proposed for the mathematical description of the process.

8. Hydroxyapatite precipitation: Growth kinetics

This chapter presents a method for determining the growth kinetics in static mixers (mixers Y) for the precipitation of hydroxyapatite. The method determines the growth kinetics based on experimental data combined with the equations of population balance model and a parameter estimation technique.

Experiments were conducted at different temperatures and supersaturations and occur in a batch reactor with mechanical agitation and temperature controlled. Solutions of calcium nitrate and ammonium phosphate were prepared using distilled water, in each was added 25% ammonia solution for pH adjustment to value 11. Flow solution of calcium nitrate and ammonium nitrate was mixed in the mixer Y using a peristaltic pump Masterflex L / S (Cole - Parmer, Germany). Particle size distribution was measured with a particle size analyzer type Saldi-7101 (Shimadzu, Japan). During the experiment, at preset time in the range 0-20 hours, samples were taken from the reactor and analyzed using the particle analyzer to determine the diameter of the particles. Mean particle diameter value is the average of two experiments (deviation 5%).

8.6. Experimental results

Concentrations were chosen in order to notice qualitatively and quantitatively the phenomena that occur in the system. In this context it may be noted that all kinetic curves obtained in the first moments exhibit a portion upward characteristic to the phenomenon of agglomeration of particles, followed by a descending portion, specific to fragmentation of agglomerates (clusters, s) formed. One can easily see that the whole field of concentration and temperature variation is a specific behavior of colloidal systems, which exhibit the phenomenon of (re) agglomeration followed by fragmentation, so that interpretation and explanation of experimental results will be made taking into account of their specific phenomenology.

Experimental results (average diameter of particles) are analyzed using a mathematical model based on the population balance equation. By combining a process model optimization algorithm based on a least squares minimization, were determined from the experimental data the growth mechanism and kinetic parameters (k_1, k_2, α) and through their assessments were made the valuation of different mechanisms of particle growth. As a conclusion we can say that in the precipitation process of hydroxyapatite are three main mechanisms:

- one specific case where physical phenomena are limitative (diffusion and physical adsorption) at high temperatures (80 °C) and very low concentrations ($k_2 = 1.1$)

- a mechanism specific for the case when the phenomena of mass conversion (polinucleation, spiral growth) are limiting the speed, a mechanism specific at low temperature (25 oC) ($k_2 > 2$)

- combined mechanism: diffusion + mass conversion, for high temperatures (40-60 oC) and low concentrations

The accuracy of model predictions can be evaluated by comparing model results with experimental data. In most cases there is a good correlation between experimental data and those obtained by simulation which confirms the accuracy of the model. It notes, however, deviations from the values obtained from the population balance model to those from experimental data, due to the effects of (re) agglomeration (this phenomenon was not included in the model). With those exceptions there is a good agreement between experimental data and those obtained by simulation, which indicates the validity of the model and the kinetic parameters determined.

9. Growth kinetics in the presence of additives

This chapter presents a method for obtaining small particles in nanometer range, which is based on a process of precipitation, realized at large supersaturation in the presence SiO2 used as surfactant. Kinetic parameters of precipitation were determined based on experimental data on the evolution in time of particle size combined with the equations a population balance model and an optimization method.

Because hydroxyapatite is used for medical purposes, the surfactant that should be added has to be biocompatible and nontoxic. This was the reason why we used SiO2 added in synthesis as sodium silicate. Since in the system occur two competing parallel reactions, experimental investigations were necessary to establish conditions under which the addition of sodium silicate should be made in the reaction mass (how to add, temperature, pH). Following experimental research, we establish technological scheme for obtaining apatites with different proportions of SiO2.

Textural and adsorptive properties of the prepared hydroxyapatite sorts have been tested on the retention capacity of copper [91] from very dilute solutions ($Cu^{2+} = 5 \cdot 10^{-3} \div 10^{-4}$ mol / l) as a future opportunity to use pure or complex apatites (containing SiO2) in remediation processes.

The results show that pure apatite leads to lower adsorption rates than apatites with structure modified by the addition of SiO2. Addition of SiO2 locks the growth of apatite particles and the phenomenon of (re) agglomeration leads to increasing their porosity, specific surface and concomitant the adsorption velocity, indicating that the process occurs on the surface of particles. The results were the prerequisite for a patent application which aims at the preparation of fungicides for agriculture, reducing substantially the amount of copper to be administered [25].

A series of experiments were carried out at different concentrations of sodium silicate to determine growth kinetics in a batch reactor. Following the procedure described in the previous chapter, the two reactants solutions were prepared which by contacting lead to hydroxyapatite with SiO_2-content.

In the ammonium phosphate solution 0.09 mol/l was added 25% ammonia solution to create highly basic medium (pH = 11), then in the solution was introduced Na_2O: SiO_2 solution, ratio 1:3,2. Simultaneously was prepared calcium nitrate aqueous solution with concentration 0.15 mol/L, and the basicity was also corrected at pH = 11. We worked at two SiO_2 concentrations: 0.075% and 0.15%. These concentrations were chosen taking into account that the SiO2 content of

hydroxyapatite from natural bone varies between 0.1 - 0.2%. During the experiment, at preset times in the range 0-20 hours, samples were taken after the procedure described in the previous chapter.

9.3. Experimental results

Experimental data obtained show that the same values are obtained for the average diameter of particles both for the proportion of 0.075% and 0.15% SiO_2 in hydroxyapatite. An explanation of the fact that nano-sized particles are obtained (0.02 μm) could be that the SiO_2 and $CaO \cdot SiO_2$ adsorbs on the particles surface, resulting in total inhibition of their growth.

The experimental results obtained were analyzed using a mathematical model based on the population balance equations. By combining a process model optimization algorithm based on least squares minimization, growth mechanism and kinetic parameters (k_1, k_2) can be determined from experimental data. The obtained model is in good agreement with experimental data and therefore can be used to design the process of precipitation. Growth mechanism has proven to be volume diffusion or volume diffusion + physical adsorption.

Additional were prepared samples of hydroxyapatite substituted with fluoride ions, the general formula $Ca_{10}(PO_4)_6(OH)_{2-x}F_x$, where 0,67<x<1,48. These fluorhydroxyapatites were deposited by the process called "flame spraying, on the surface of magnesium alloys [105]. by Scanning electron microscopy (SEM) characterization indicate the possibility of achieving uniform layers of fluorhydroxyapatite with thicknesses of 50 μm. IR analysis of the deposits show that fluoride ions entered the structure of hydroxyapatite, thus increasing its thermal stability as shown by X-ray diffraction analysis. Finally, by adding fluorine to obtain different apatite-based materials that can be successfully used in coatings for magnesium alloys. Preliminary research carried out indicates the possibility of broadening the range of biomaterials based on apatites / apatites substituted with fluorine.

10. Personal contributions

Recent studies show that in literature are no data about mathematical modeling of processes components in the technology for obtaining hydroxyapatites. Also there are missing data about the use of mathematical models as tools for control, predictive control and management of hydroxyapatites-based biomaterials technology. The novelty of this thesis is to attempt to achieve such a study for the synthesis of hydroxyapatite and its substituted derivatives (with SiO2) by precipitation. The thesis presents a clear centralization of the main phenomena occurring during the precipitation and the aspects to be taken into account in developing the mathematical model of the process.

Based on kinetic study undertaken in this study a mathematical model of the transformation of amorphous calcium phosphate into hydroxyapatite was elaborated. Process simulation using the mathematical model shows that it can be described by the equation: $\eta = 1 - e^{-K_2 \cdot \tau^2}$, that corresponds to a combined macrokinetic mechanism.

In the thesis was presented a method for measuring the kinetics of crystal growth and fragmentation of agglomerates and was developed a mathematical model of the precipitation process of hydroxyapatite. The method is based on the measurement of particle size at different residence time in reactor. By combining the mathematical model based on the population balance equations with an optimization algorithm based on least squares minimization, we determined the growth mechanism and kinetic parameters (k_1, k_2, α) from the experimental data and through their assessments were established the different mechanisms of particle growth.

Following experimental research, we establish technological scheme for obtaining apatites with different proportions of SiO2, a technique for producing nanoparticles. The installation comprises a mixing batch reactor and a static mixer Y, which allows rapid mixing of reactants at high levels of supersaturation. Preliminary studies were made for a series of samples with fluoride ions substituted hydroxyapatite (fluorhydroxyapatite). They proved to be sufficiently thermally stable and can be used in the coating process called "flame spraying".

In the thesis has been proposed three functional forms for function of the fragments distribution (the 3 cases of fragmentation of the particle) and fragmentation coefficients were determined – an information key in solving the population balance equation.

The mathematical model established in this thesis will be used later to develop a complex mathematical model/ product (software) that will allow optimization of working parameters and control, automatic control and predictive management of the process of obtaining hydroxyapatite. The results will contribute to the broad scientific knowledge and a priority area of great interest nationally and internationally. The literature study shows that both national and international communication between groups of specialists in engineering and materials science is very weak, research articles are limited to very restricted areas of specialty.

11. Concluding remarks

This paper presents a method for determining the kinetic parameters for the precipitation process of hydroxyapatite. The method is based on the measurement of particle size distribution in different working conditions using a particle analyzer. Growth mechanism of particles identified was a combined one, and is consistent with the literature.

In the thesis is presented the method of obtaining by precipitation nano-particles of hydroxyapatite and the protocol used for determining growth rate in these conditions. This technique involves the use of surfactants, whose role is to inhibit crystal growth and to stabilize the particles by reducing the phenomenon of (re)agglomeration. Sodium silicate was used as the additive, in two different concentrations.

The mathematical model of the transformation of amorphous calcium phosphate into hydroxyapatite was established and were determined the numerical values of the constant from mathematical model. Simulation model validation process was done by using the proposed model. The values obtained match well with experimental data which confirms the accuracy of the model.

As a general conclusion, we observed that:
- high temperature decreases the phenomenon of agglomeration of particles (simulation didn't take into account the (re) agglomeration)
- addition of surfactants blocks particle growth and (re) agglomeration phenomenon disappears
- at high temperatures the conversion rate of amorphous calcium phosphate into hydroxyapatite is higer
- for the synthesis of hydroxyapatite optimal pH is 11

The mathematical model obtained in this thesis provides background information for the development of methods for determining the kinetic parameters of growth and fragmentation for the precipitation of hydroxyapatite based on the measured particle size distribution. Because very high superaturation, nucleation is instantaneous, very difficult to control, the technical means that are currently available in the laboratory did not allow separate study of this process. This is why we studied the overall precipitation process: nucleation - growth of germs - fragmentation. The fact that the mathematical model agrees well with experimental data, shows that the modeling of this process is possible. The mathematical model obtained will be included in a complex model, which can then be used in process

control in order to obtain materials with controlled properties for various applications. This approach is very topical and it is not common in materials science.

Bibliography

1. Zauner R., Jones A. G., Scale-up of conţinuous and semibatch precipitation processes, Ind. Eng. Chem. Res., 39, 2392-2403, 2000

2. Wei H. and Garside J., Application of CFD modelling to precipitation systems, Trans. IChemE., 75, 219–227, 1997

3. Bałdyga J., Orciuch W., Barium sulphate precipitation in a pipe – An experimental study and CFD Modeling, Chem. Eng. Sci., 56, 2435-2444, 2001

4. Marchisio D. L., Barresi A. A., and Fox R. O., Simulation of turbulent precipitation in a semi-batch taylor - couette reactor using CFD, AICHE J., 47, 664-676, 2001

5. Phillips R., Rohani S., and Bałdyga J., Micromixing in a single- feed semi-batch precipitation process, AICHE J., 45,82-92, 1999

6. Wei H., Wei Z. and Garside J., Computational Fluid Dynamics - Modeling of the precipitation process in a semibatch crystallizer, Ind. Eng. Chem. Res., 40, 5255-5261, 2001

7. Jaworski Z., and Nienow A. W., A strategy for solving a mathematical model of barium sulfate precipitation in a conţinuous stirred tank reactor, Chem. Eng. Res. Des., 82, 1089–1094, 2004

8. Kresta S., Anthieren G., Parsiegla K., Model reduction for prediction of silver halide precipitation, Chem. Eng. Sci., 60, 2135–2153, 2005

9. Mersmann A., Crystallization and precipitation, Chem Eng Proc., 38, 345-353, 1999

10. Elimelech M, Jia X, Gregory J, Williams RA., Particle deposition and aggregation: measurement, modelling and simulation., Woburn MA: Butterworth-Heinemann, 1998

11. Zukoski CF, Rosenbaum DF, Zamora PC., Aggregation in precipitation reactions: stability of primary particles, Chem. Eng. Res. Des., 74, 723-731, 1996

12. Schwarzer H-C, Peukert W., Experimental investigation into the influence of mixing on nanoparticle precipitation., Chem Eng Tech., 25, 657-661, 2002

13. Judat B, Kind M., Morphology and internal structure of barium-derivation of a new growth mechanism, J Colloid Interface Sci., 269, 341-353, 2004

15. Zahouily M., Abrouki Y., Bahlaouan B., Rayadh A., Sebti S., Hydroxyapatite: new efficient catalyst for the Michael addition, Câtal. Commun., 4, 521-524, 2003

16. Nishikawa H., Radical generation on hydroxyapatite by UV irradiation, Mater. Lett. 58, 14-16, 2003

17. Liptáková B., Hronec M., Cvengrosová Z., Direct synthesis of phenol from benzene over hydroxyapatite catalysts, Catal. Today 61, 143-148, 2000.

18. Ho C.M., Yu W.Y., Che C.M., Angewandte Chemie (International Edition), v. 43, 3303-3307, 2004

19. Sebti S., Tahir R., Nazih R., Saber A., Boulaajaj S., Hydroxyapatite as a new solid support for the Knoevenagel reaction in heterogeneous media without solvent, Appl. Catal. A Gen., 228, 155-159, 2002

20. Melde, B.J.; Stein, A. Periodic Macroporous Hydroxyapatite-Containing Calcium Phosphates, Chem. Mater., 14, 3326 - 3331., 2002

21. Paul W., Sharma C.P., Development of porous spherical hydroxyapatite granules: application towards protein delivery, J. Mater. Sci. Mater. Med., 10, 383-388, 1999

22. Z.L. Huang, D.W. Wang, Y. Liu, Y. Zhang, J. Wei, Y.L. He, Chinese, J. Inorg. Mater. 17 (2002) 959.

23. Bogya E.S., Bâldea I., Barabás R., Csavdári Al., Turdean G., Dejeu V.R., Kinetic studies of sorption of copper(II) ions onto different calcium-hydroxyapatite materials, Studia Chemia, XLV, 2, TOM II, 363-373, 2010

24. Barabás R., Pop. Al., Paizs Cs.: Compoziţii fungicide pe bază de săruri de zinc, mangan şi fier ale acidului N,N-etilen-bis-tiocarbamic şi procedeu de obţinere, no 817, 2009

25. Barabás R., Pop Al.: Compoziţii de fungicide cuprice de înaltă dispersie şi procedeu de obţinere, no 1037610, 2009

26. Mitre V., Miclauş V., Mitre I., Drăgan S., Pop A., Barabás R.: Procedeu de obţinere a unei compoziţii de îngraşamânt foliar pe bază de calciu, no 1053694,

27. Barabás R., Pop A., Bogya E., Dejeu V., Mitre V., Mitre I.: Procedeu de obţinere a unei compoziţii de îngrăşământ foliar pe bază de azot, fosfor şi potasiu, no 397, 2008

28. Vallet-Regi M., Ceramics for medical applications, J. Chem. Soc., Dalton Trans., 97-108, 2006

29. Bernarda, L., Frecheb, M., Lacoutb L.J., Biscans, B., Modeling of the dissolution of calcium hydroxyde in the preparation of hydroxyapatite by neutralization, Chem. Eng. Sci., 23, 5683 – 5692, 2000

30. Tancreta, F., Boulerb, J.-M., Chamousseta, J., Minoisa, L.-M., Modelling the mechanical properties of microporous and macroporous biphasic calcium phosphate bioceramics, J. Eur. Ceram. Soc., 16, 3647-3656, 2006

31. Gerstlauer A., Motz S., Mitrovic A., and Gilles E. D., Development, analysis and validation of population models for conţinuous and batch crystallizers, Chem. Eng. Sci., 57, 4311– 4327, 2002

32. Randolph A. D. and Larson M. A., A Population Balance for Countable Entities, Can J Chem Eng, 42(6), 280–281, 1964

33. Hulburt H. M. and Katz S. L. , Some Problems in Particle Technology, A Statistcal Mechanical Formulation, Chem. Eng. Sci., 19, 555–574, 1964

34. Ramkrishna D., Population Balances: Theory and Applications to Particulate Systems in Engineering, Academic Press, San Diego, 2000

35. Ramkrishna D.,The status of population balances, Rev. Chem. Eng., 3, 49-95, 1985

36. Song M. and Qiu X. J., An alternative to the concept of the interval of quiescence (iq) in the monte carlo simulation of population balances, Chem. Eng. Sci., 54, 5711-5715, 1999

37. Singh P. N. and Ramkrishna D., Solution of population balance equations by MWR, Comput Chem. Eng., 1, 23-31, 1977

38. Ryall R. L., Hounslow M. J. and Marshall V. R., A discretized population balance for nucleation, growth, and aggregation, AIChE J., 34, 1821-1832, 1988

39. Randolph A. and Larson M.A., Theory of particulate processes, Academic Press, Inc., San Diego, CA, 2nd edition, 1988

40. Dirksen JA, Ring TA., Fundamentals of crystallization: kinetics effect of particle size distribution and morphology, Chem. Eng. Sci., 46, 2389-2427, 1991

41. Mersmann A., Crystallization Technology Handbook, editor Marcel Dekker Inc., New York, 2nd edition, 2001

46. Mullin J. W., Crystallization, Elsevier Butterworth–Heinemann, 2001

49. Flood A.E., Thoughts on recovering particle size distributions from the moment form of the population balance, Dev. Chem. Eng. Mineral Process., 10, 501-519, 2002

50. Lindenberg C., Schöll J., Vicum L., Mazzotti M., Brozio J., L-Glutamic Acid Precipitation: Agglomeration Effects, Cryst. Growth Des., 8, 224–237, 2008

51. Myerson A. S., Handbook of Industrial Crystallization, 2nd edition, Butterworth-Heinemann, 2001

53. Jones A., Crystallization Process Systems, Butterworth-Heinemann, 2002

73. Dejeu V. R., Barabás R., Pop Al., Bogya E.S., Agachi P.-Ş., Kinetic studies for the transformătion process of beta-whitlockite in hydroxyapatite, Revista de chimie, 12, 1251-1253, 2009

91. Bogya E.S., Barabás R., Dejeu V. R., Csavdari Al., Baldea I., Hydroxyapatite modified with SiO2 used in retaining processes of Cu2+ ions, Chem. Pap., Chemicăl Papers, 63 (5), 568–573, 2009

105. Barabás R., Bogya E.S., Dejeu V. R., Bizo L., Fluorhydroxyapatite coatings obtained by flame spraying deposition, Int. J. Appl. Ceram. Technol., 1–6, DOI:10.1111/j.1744-7402.2009.02480.x, 2010