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SIMULATION ENVIRONMENT FOR POLYMERIC NANOPARTICLE: EXPERIMENT DATABASE[1]

AMBIENTE DE SIMULAÇÃO PARA NANOPARTÍCULAS POLIMÉRICAS: REPOSITÓRIO DE EXPERIMENTOS

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ABSTRACT

Simulations in the Nanoscience area are widely used and the validation processes are generally associated with scientific or mathematical models. This paper shows design and implementation of experiments management module, as part of a simulation environment for nanoparticles. The module is part of a larger project named Multiagent System for Polymeric Nanoparticles (MASPN). The simulations, which have run in MASPN, need validation, so the importance of an experiment database for correlation. This database can support evaluation of stable formulations, behaving as a pattern recognition tool. The simulation environment, such as a software tool, was designed and implemented following the software engineering methodology known as Feature-Driven Development (FDD). The results were the assessment of requirements and system input parameters; modelling and diagramming of MASPN features; system graphical interfaces; particle distribution display (size and position); and normal distribution charts display. Moreover, it is emphasized the possibility of correlation between experimental results and theoretical simulations.

Keywords: feature-driven development, nanomaterials, nanocapsules, software engineering.

RESUMO

As simulações em Nanociência são utilizadas amplamente e os processos de validação estão relacionados com modelos matemáticos. O artigo apresenta o projeto e a implementação do módulo de gerenciamento de experimentos inserido no ambiente de simulação MASPN. As simulações que são executadas no ambiente necessitam de validação, por isso a importância de uma base de dados para a correlação. Esse banco de dados fornece suporte à avaliação das formulações estáveis, comportando-se como uma ferramenta de reconhecimento de padrões. O ambiente de simulação, como uma ferramenta de software, foi projetado e implementado seguindo a metodologia Feature-Driven Development (FDD). Os resultados obtidos foram o levantamento de requisitos e os parâmetros de entrada do sistema; modelagem e diagramação das funcionalidades do MASPN; interfaces gráficas do sistema; exibição de distribuição de partículas (tamanho e

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posição); e exibição dos gráficos de distribuição normal. Além disso, destaca-se a possibilidade de correlação entre os resultados experimentais e simulações teóricas.

Palavras-chave: *engenharia de software, feature-driven development, nanomateriais, nanocápsulas.*

INTRODUCTION

Research in Nanotechnology presents the creation of experimental and computational tools for the design and construction of nanostructures, such as nanowires, nanosensors, nanocatalysts, nanocarriers and so on. (VILELA NETO, 2014). These nanoparticles have particle dispersions or solid particles with much larger surface area than its volume; in other words, the majority of their atoms are disposed on the surface of the material. Thus, the nanoparticles are ideal for applications in composite materials, drug delivery, for example (BARUA; MITRAGOTRI, 2014). Besides, when investigating the universe at a very small scale, the self-organizing ability of the particles or matter is very similar to what happens with the biological entities - the mechanisms respond to environmental stimuli without the need for conscious control (DOWLING; CLIF; GROBERT, 2004).

According to Ntika, Kefalas and Stamatopoulou (2013), the nanoparticles can carry a drug charge, and because of its size, they can escape the detection of the immune system. In contrast, a compound formed by nanoparticles (nanoparticulated system) may produce agglomeration; therefore, this system will be unstable (JO et al., 2015), since it does not ensure the desired properties, such as size, surface area and sedimentation characteristics.

So one challenge is to track, describe or even predict the behaviour of nanostructures, especially the agglomeration behaviour. For that, the computer simulation is a way to evaluate the self-organizing behaviour of matter (BARBOSA; KROTT; BARBOSA, 2016; VILELA NETO, 2014). However, the simulation method comprises a very important step - validation of results. This validation process ensures that the simulation results represent the reality of the simulated environment. Results of validation processes are generally associated with scientific or mathematical model database. The simulation environment MASPN (Multi-agent System for Polymerics Nanoparticles) aims to evaluate the agglomeration effect of polymeric nanoparticles (ZAMBERLAN; FAGAN, 2015; ZAMBERLAN; BORDINI; FAGAN, 2015), but the environment (or tool) does not have a module to validate the simulations following mathematical or analytical method. Thus, an experiment database for correlation is important for all the simulation process. This database can support the evaluation of stable formulations, behaving as a pattern recognition tool.

Therefore, in this paper, the experiment management module to support the validation process in MASPN is presented. As a result, modelling of environment and system interfaces are detailed in accordance with the Feature-Driven Development (FDD) method.

Finally, the paper is divided into five sections to facilitate understanding. The next section covers the concepts related to polymeric nanoparticles, discussing physicochemical parameters and the agglomeration effect. In the Materials and Methods section we present some tools used to design and implement the simulation environment.

POLYMERIC NANOPARTICLES

Polymeric nanoparticles are defined as polymeric colloidal suspensions, which include nanospheres and nanocapsules; these are prepared by polymerization methods (synthesis of polymers) or through pre-formed polymer (BAGUL; MAHAJAN; DHAKE, 2012; MOHANRAJ; CHEN, 2006; WILCZEWSKA et al., 2012).

A polymeric coating disposed to surrounding an oil core forms Nanocapsules. The drug may be dissolved in this core and/or adsorbed to the polymeric wall. On the other hand, nanospheres, which do not have oil in their composition, are formed of a polymer matrix, where the drug may be trapped or adsorbed (BAGUL; MAHAJAN; DHAKE, 2012). Polymeric nanoparticles are generally formed by surfactants, in order to reduce the surface tension (WILCZEWSKA et al., 2012).

Therefore, polymers must protect the drug from degradation or metabolism, promoting sustained release of the drug by keeping concentrations of plasma at therapeutic levels for certain periods of time (JO et al., 2015).

Although liposomal nanoparticles have been used as potential carriers, polymeric nanoparticles stand out due to their specific advantages over liposomes by increasing the stability of the encapsulated drugs. Polymeric nanoparticles have sustained release properties of the drug, an increased encapsulation efficiency and an increased storage stability (BAGUL; MAHAJAN; DHAKE, 2012).

A key feature of these nanoparticles is its size, usually within the limits of approximately 1000 nm (JO et al., 2015), although variations average obtained is 100-500 nm (MORA-HUERTAS; FESSI; ELAISSARI, 2010).

In a study fulfilled by Mora-Huertas, Fessi and Elaissari (2010), and Bagul, Mahajan, Dhake (2012), there are compilations of some advantages of using nanoparticles: drug delivery mechanisms; the subcellular size allows a higher absorption than other particulate systems; stability of active substances; biocompatibility with tissue cells and synthesized from materials that are biocompatible or biodegradable. Thus, polymeric nanoparticles have been extensively studied as drug carriers in the pharmaceutical field (JO et al., 2015).

However, over time, agglomeration can occur in the suspensions, and thus causing sedimentation (unstable suspensions). There are factors that influence the stability of the suspensions, for example adsorption active molecules to the surface of the nanoparticles and the presence of

surfactants adsorbed. Moreover, evaluate this agglomeration effect or stability is quite important, because it can check the toxicity of the particles at the nanoscale, considering that this effect alters the size, surface area and sedimentation properties of nanoparticles (MORA-HUERTAS; FESSI; ELAISSARI, 2010). Therefore, if the produced nanostructured system expresses agglomeration, it will lose its purpose, for example, the ability to not be detected by the immune system (stealth mode) and the ability to deliver a particular drug to the predetermined target in the human body.

Schaffazick et al. (2003) have listed some physicochemical parameters that can be used to monitor the stability of such polymeric colloidal suspensions, which is called the agglomeration effect. Such parameters are particle size, particle size distribution, zeta potential (or electric charge surface), molecular weight distribution of the polymer, drug content, pH, and encapsulation efficiency. Under these circumstances, an attractive property of nanoparticles is the possibility to control size, shape (not addressed in this study), and surface characteristics of these particles (JO et al., 2015).

PHYSICOCHEMICAL PARAMETERS AND THE EFFECT OF AGGLOMERATION

In this paper, it is assumed that agglomeration occurs when the particles are distributed freely into assembly that can simply be broken by mechanical forces. Aggregation[8] is a defined pattern of molecules, which can be in any physical state (NICHOLS et al., 2002). Agglomeration is a contact process and adhesion, which dispersed particles remain together by weak physical interactions, being a reversible process (MCNAUGHT; WILKINSON, 1997). Nanoparticles may agglomerate or aggregate when inserted in an environment or biological fluid. But agglomeration often occurs when there is high ionic strength that protects the repulsion due to electric charge on the nanoparticles. Therefore, monitoring the effect of agglomeration, as mentioned before, is essential (MORA-HUERTAS; FESSI; ELAISSARI, 2010; WILCZEWSKA et al, 2012). The characterization of nanostructures occurs in an experimental laboratory, and some are analysed by computer simulation (VILELA NETO, 2014). In the following, the main parameters evaluated in the nanoparticles characterization, and the relationship with the effect of agglomeration are described.

Particle size

The particle size and size distribution (percentage of particles with specific size) are important characteristics of the nanoparticle systems (JAIN; MEHRA; JAIN, 2014). Bagul, Mahajan and Dhake (2012) state that the fastest and usual methods for determining the particle size are Photon-Correlation Spectroscopy (PCS) or Dynamic Light Scattering (DLS). PCS determines the particle diameter by

[8] According to Nichols et al., (2002 p.2103), each term has a specific meaning, but unfortunately, they are often exchanged and this resulted in confusion.

Brownian movement and by the light scattering properties. However, the method that requires the viscosity of the medium must be known. The results of PCS are usually checked by means of Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) (MOHANRAJ; CHEN, 2006).

Nanoparticles have a higher risk of agglomeration during nanoparticle drug delivery. And it is a challenge to formulate structures with the smallest possible size and maximum stability (BAGUL; MAHAJAN; DHAKE, 2012; MOHANRAJ; CHEN, 2006).

Zeta potential

The ionic strength of a solution influences the electrical charge of the surface (zeta potential) of particulate structures. The liquid charge on particle surface affects the distribution of ions in its neighbourhood, as this increases the concentration of contra-ions close to the surface. Thus, it forms a double electrical layer on the particle surface with the liquid.

In accordance with Bagul, Mahajan and Dhake (2012), the zeta potential is usually used to characterize the charging property of the surface of the nanoparticles. It reflects the electric potential of the particles and it is impacted by composition of the particle and the medium in which it is dispersed. A particle is electrically charged when it has a small amount of unbalanced charge. Electrically charged objects interact exerting (generating) forces of attraction or repulsion on each other. All particles observed have a charge that is a multiple integer of the elementary charge

$$e = 1{,}602 \times 10^{-19}\ \mathrm{C} \qquad (1)$$

Hence, it is assumed that the charge of any object is always a multiple integer of the elementary charge and the electric force between two charges with the same sign is repulsive, and while the electric force between two charges with opposite signs is attractive. Thus, charged particles are stabilized when there is repulsion, and they will get agglomerated when there is attraction. Mora-Huertas, Fessi and Elaissari (2010) argue that there is no specific trend of zeta potential on the behaviour of polymeric nanoparticles. For example, the zeta potential of the nanocapsules depends on the chemical nature of the polymer, the chemical nature of the stabilizing agent and the pH.

pH

Schaffazick et al. (2003) claim the relevant information about stability of nanoparticulate suspensions may be obtained by monitoring the pH, over time. In general, pH values of the nanocapsules are dispersed within a range of 3.0 to 7.5. According to Mora-Huertas, Fessi and Elaissari (2010) pH of dispersion determines the zeta potential of colloidal dispersions, which may have some impact on

their stability. The pH of the dispersion appears to be a key factor controlling the size the nanoparticles and, consequently, its biodistribution.

Drug Content

The association rate (or drug content) refers to the amount of drug associated with nanoparticles, but the determination of the amount of associated drug is particularly complex due to the small size of these nanostructures, which makes the separation of free drug fraction of the associated fraction (MOHANRAJ; CHEN, 2006). When the drug concentration is greater than the saturation (point of maximum concentration) nanocrystal drugs can be formed concurrently with the nanocapsules in the preparation process. Thus, after the drug entrapment in nanocoating, there may be the effect of agglomeration of these nanocapsules (precipitation) due the initial agglomeration of drug nanocrystals (GUTERRES et al., 1995). Thus, according to Pohlmann et al. (2008), the drug content influences the agglomeration effect (or instability of concentration), because the nanocrystals formed in formulations agglomerate and precipitate during storage of nanocapsules in the course of time.

CONSIDERATIONS ON THE PHYSICO-CHEMICAL PARAMETERS

According to Filho and Sierra (2015), in order to obtain a stable colloidal suspension (PNs) requires certain conditions and those are identified in accordance with the DLVO theory (Deryagin, Landau, Verwey and Overbeek). This theory deals with the balance between attractive and repulsive forces among the particles in suspension. Thus, it can be stated that a polymeric nanoparticulate system will be more stable if the repulsive forces acting between its particles are more intense.

Table 1 illustrates the main polymers handled in this paper, the association of such polymers with specific drugs to be encapsulated, the empirical parameters discussed so far and the final relationship with the agglomeration effect (or instability). This compilation serves as a reference for the desired simulation, especially for assessing environmental behaviour simulation proposed since each drug-polymer has been reported in scientific studies.

Finally, this discussion of physical-chemical parameters and the relationship to agglomeration effect, it can be concluded that there is migration of the chemical volume to surface chemistry (phenomenon consequence of nanoscale). Besides, it is possible to see that some parameters influence others, almost in a circle way. For example, the size directly influences the stability of the solution, but it is dependent on the drug contents. On the other hand, the ionic strength and pH of environment modify the zeta potential, which also acts directly on the effect of particle agglomeration and is considered a key indicator of stability in colloidal dispersions.

Table 1 - Relationship between polymer-drug and parameters-stability.

Polymer	Drug	Drug content (mg / mL)	Size (nm)	Zeta potential (mV)	pH	Stable	Reference
Eudragit RS 100	Clotrimazole	1 3	169 ± 15 173 ± 12	14.5 ± 2.5 14.4 ± 3.0	5.7 ± 0.1 5.6 ± 0.1	Yes Yes	Santos et al. (2014)
Eudragit RS 100	Dihydromyricetin	1 2 5	161 ± 2.5 151 ± 0.7 123 ± 1.0	11.4 ± 0.6 12.7 ± 0.4 13.4 ± 1.0	5.6 ± 0.04 4.2 ± 0.01 3.8 ± 0.01	Yes Yes No	Dalcin (2015)
PCL	Nisin	1	234 ± 6.0	-6.62 ± 0.42	5.3 ± 1.32	Yes	Abreu et al. (2016)
PCL	Tretinoin	0.5	228 ± 0.8	-7.27 ± 0.66	6.6 ± 0.31	Yes	Ourique et al. (2008)
PLGA	Sparfloxacin	1	210 ± 3.8	22.8 ± 1.3	ND	Yes	Gupta et al. (2010)
Eudragit RL 100	Anfotericin B	1	263 ± 4.0	30.2 ±0.2	ND	Yes	Das, Suresh and Desmukh (2010)
Chitosan	Pravastatin	1 2.5 5.0 7.5 10.0	159 ± 13 170 ± 15 185 ± 17 247 ± 20 270 ± 23	30.2 ± 2.5 20.6 ± 3.1 32.1 ± 3.1 25.2 ± 2.3 25.6 ± 3.4	ND	Yes Yes Yes No No	Bradan et al. (2016)
PLA	Curcumin	5 10	127 ± 1.9 258 ± 05	ND	ND	NI	Mazzarino et al. (2010)
PLA + Pluronic F 68	Curcumin	2.5 5.0	249 ± 1.1 502 ± 0.7	ND	ND	NI	Mazzarino et al. (2010)
PLA + Solutol HS15	Curcumin	2.5 5.0	256 ± 0.7 509 ± 0.5	ND	ND	NI	Mazzarino et al. (2010)

*ND = Not determined

*NI = Not informed

MATERIALS AND METHODS

The MASPN (simulation environment) aims to assess structural and functional aspects of nanoparticles, in order to monitor the agglomeration effect. For this, it is important to manage experimental data carried out in laboratory; generate graphs of particle size distribution, zeta potential and pH; generate particles interaction animations; illustrate the size distribution and particle position.

The simulations should be validated by a repository of experiments previously stored, containing data such as number of particles, maximum size and minimum particle average size distribution, zeta potential, drug content, pH and the final result of the solution (stable or not). Thus, a simulation environment is required to manage experiments, display graphs illustrating simulation results for animations.

Therefore, we used the software development methodology known as Feature-Driven Development. The FDD has five processes, divided into two phases (design and planning; construction). The first phase has three processes in order to develop an overall model by listing and planning the features and system requirements. In the second phase, it is discussed the construction of the project, always interactively, incrementally and by visual diagrams (PRESSMAN, 2010).

For the design and implementation of the simulation environment, some tools were used:

- BonitaBPM[9] (System for diagramming processes based on Business Process Modeling Notation[10] (BPMN));
- Astah[11] (Environment for diagramming structural and functional aspects of system based on Unified Modeling Language[12] (UML));
- Netbeans[13] (Integrated Development Environment (IDE) that allows applications to be developed from a set of component modules);
- Java Development Kit[14] (JDK) (the Java language platform that has packages, classes and operations for building a system);
- JFreeChart[15] (collection of reusable classes for building graphics);
- SQLite[16] (database management system, without the mechanism client-server database).

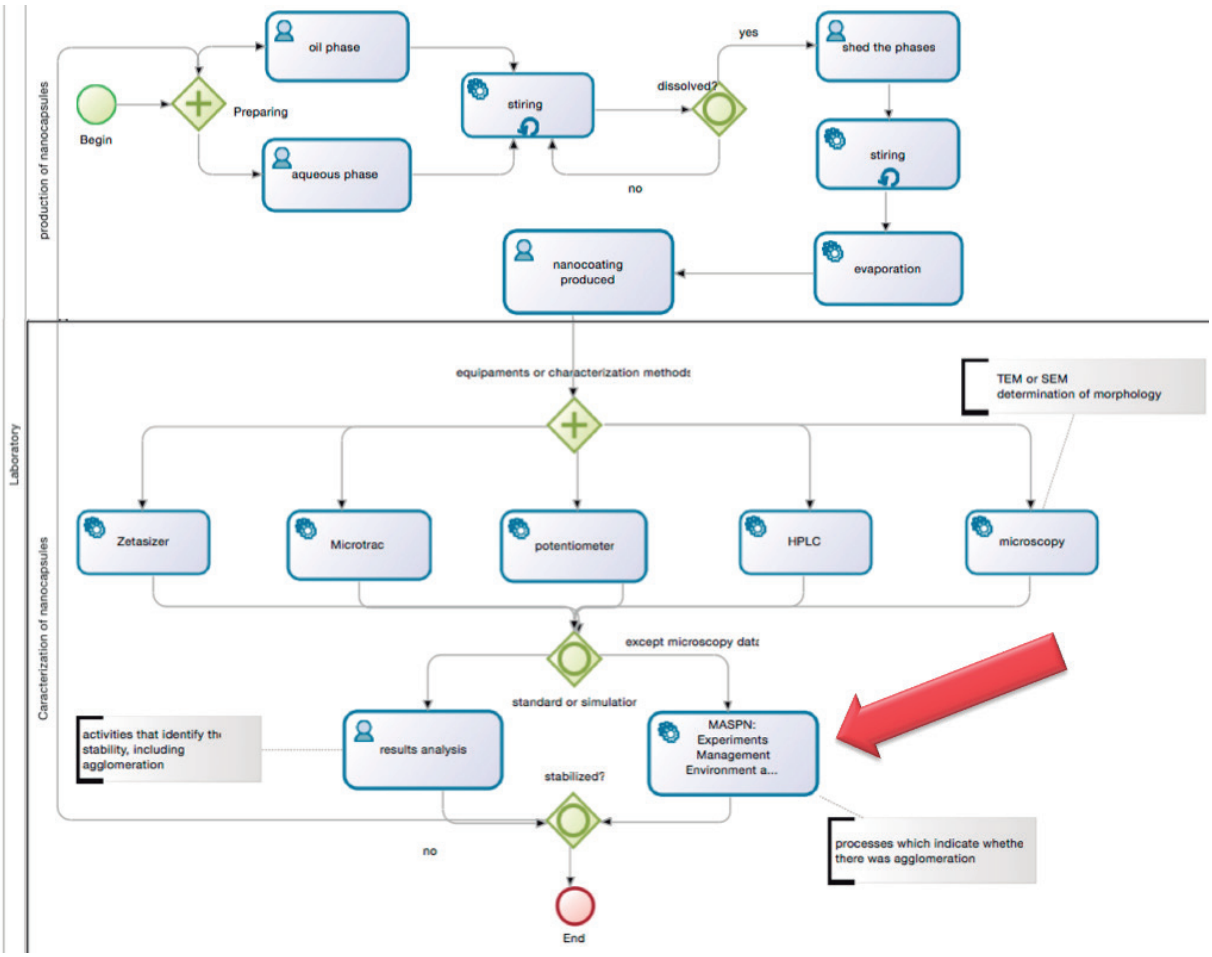
RESULTS AND DISCUSSIONS

According to the FDD method, the first phase "Initial Modelling" aims to develop a general model. Thus, figure 1 illustrates the production processes and characterization of nanocapsules in accordance with the Business Process Modelling Notation (BPMN). In the modelling illustrated in the diagram it is possible to visualize the moment the designed simulation environment (MASPN) can be used. After the nanocapsule is produced, there is the characterization process. At this stage, numerous methods and techniques are used to verify and validate the key parameters such as size, pH,

[9] <http://bonitasoft.com>
[10] <http://www.bpmn.org>
[11] <http://astah.net/editions/community>
[12] <http://www.uml.org>
[13] <https://netbeans.org>
[14] <http://www.oracle.com/technetwork/java/index.html>
[15] <http://www.jfree.org/jfreechart>
[16] <http:// www.sqlite.org>

zeta potential, etc. The results are analysed by professionals able to understand if the solution produced is adequate or not, i.e., stable. At this point the simulation environment would be a professional support tool.

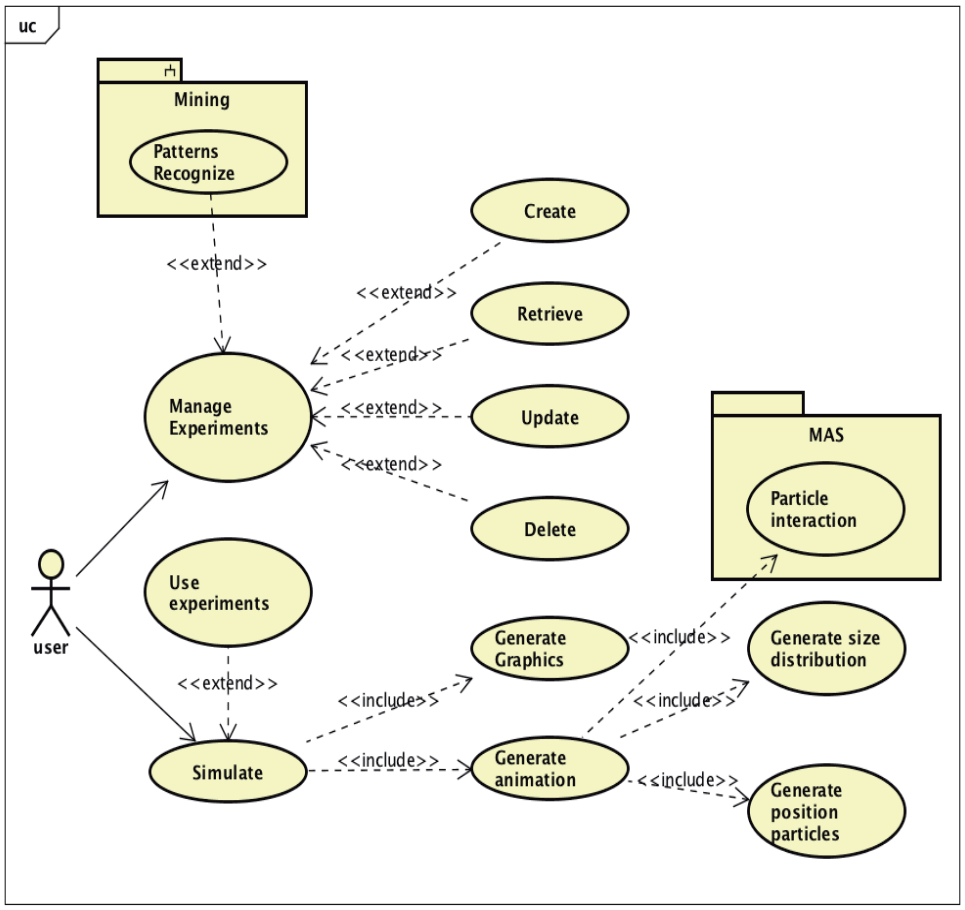
Figure 1 - Production and characterization of Polymerics Nanoparticles.



It should be noted that the data used in simulations in the MASPN do not originate from the production process and characterization in the laboratory, but from published data according to table 1. Once this has been done, the laboratory data can be entered into the MASPN that will correlate with the data of scientific publications previously stored.

Following the FDD guidelines, even in the first stage and complementing the overall model, it is necessary to list and plan the system features. Thus, the main features of MASPN are in figure 2, where the system user can manage and simulate experiments. It may be noted that in the feature "Manage Experiments", due to database, it is possible to identify patterns in experiments as: which polymer, with a particular drug at any concentration, has a stable result. This feature is within the subsystem "Mining", represented by the use case "Patterns Recognize".

Figure 2 - Use case diagram: MASPN features.



The feature “Manage Experiments” has resulted in the Experiments Management Interface (Figure 3), which exemplifies the stored experiments (DALCIN, 2015) in the database. In Experiments Interface it is possible to load files:

- publication in which the experiments were published (“Load Paper” button);
- data about particle size, zeta potential and pH generated by the equipment Zetasizer (“Load Sizes”, “Load Zetas” and “Load pHs” buttons).

The data stored in the database can be used in comparison with data collected in the laboratory (experimental results). The experiment management module performs and represents the validation process, since there is correlation of the simulation with the stored data. Figure 4 illustrates the idea of the correlation process.

Figure 3 - Experiments Management Interface - control of publications and experiments.

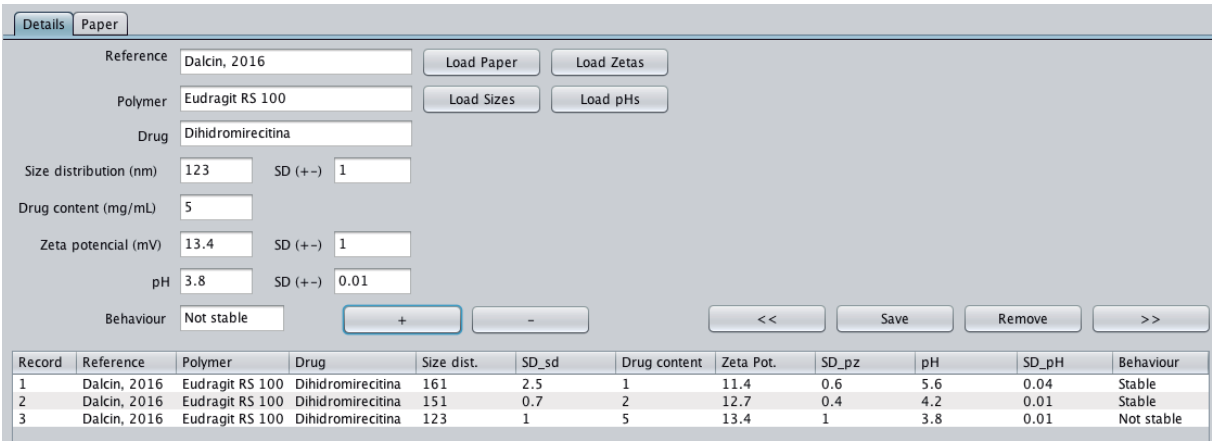


Figure 4 - General view of simulations validation.

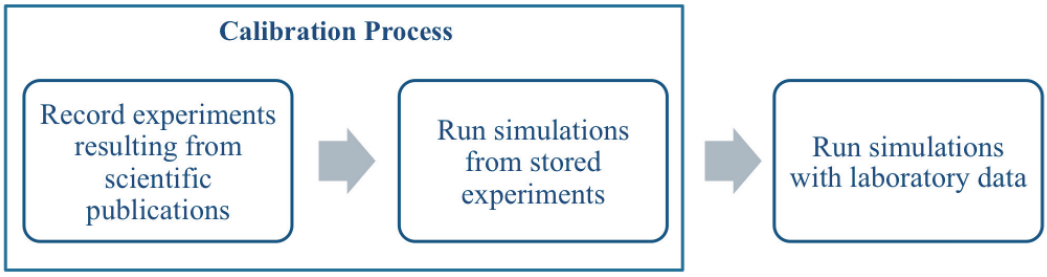


Figure 5 illustrates the main Graphical User Interface. The User can select a stored publication and a specific experiment. It is possible to generate simulation ("Generate" button). At this time, the features "Simulate", "Generate Graphics", "Generate Size Distribution" and "Generate Position Particles" are triggered.

Figure 6 shows the class diagram - structural aspects of the proposed system - where it is possible to see classes (files containing codes) responsible for the implementation of all planned features.

The *JFrameMain* class is the management of the application and it is through it that the other operations are executed. The *JFrameManageExperiments* class is responsible for managing (creation, updating, reading and removal) of the experiments from the database.

The *Draw* class is responsible for generating and drawing particles in a distributed manner, following the parameters informed/loaded in the main interface (amount of particles, minimum size, maximum size, distribution size and standard deviation).

Figure 7 illustrates the idea of particle interaction. Each particle will have different radius of coverage (or perception) of surface electric charge, drug content and molar mass, always obeying the environment ionic strength and pH. If the quantity of particles or the size of particles changes, these radii should influence the perception of the entire system. The coverage radius is measured from the centre of the particle towards its periphery.

Figure 5 - Initial Interface MASPN.

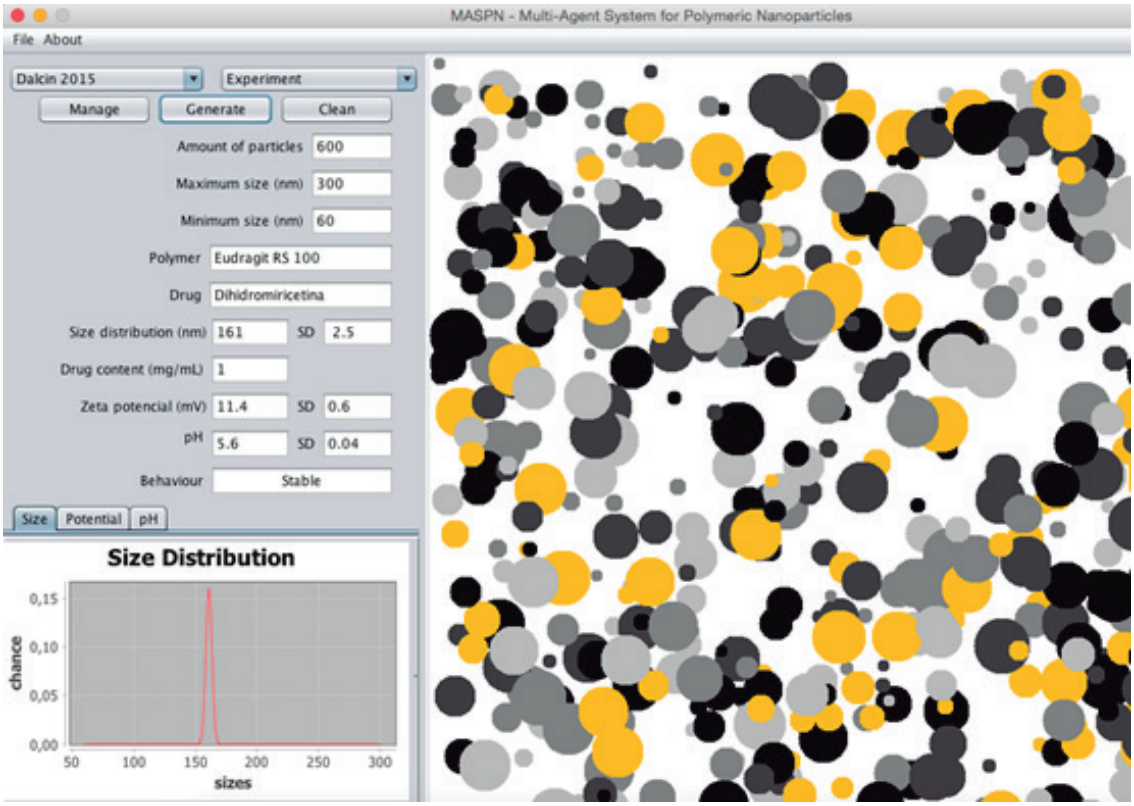
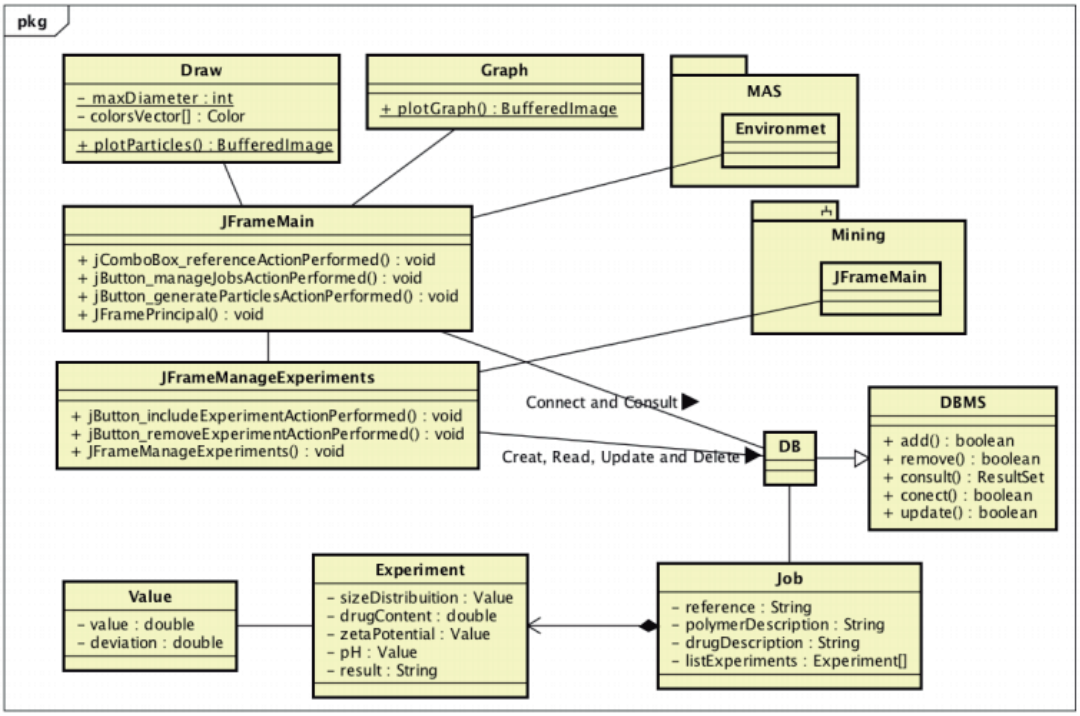


Figure 6 - Class Diagram.



The *Graph* class generates and draws the distribution graph in the main interface. Again, it has as parameters the loaded experiments file in Experiments Management Interface. This file contains all particle sizes, a process carried out in the Zetasizer equipment. The *Job*, *Experiment* and *Value* classes represent the handled data structures throughout the system processing.

Figure 7 - Interaction Idea: perception radius ratio.

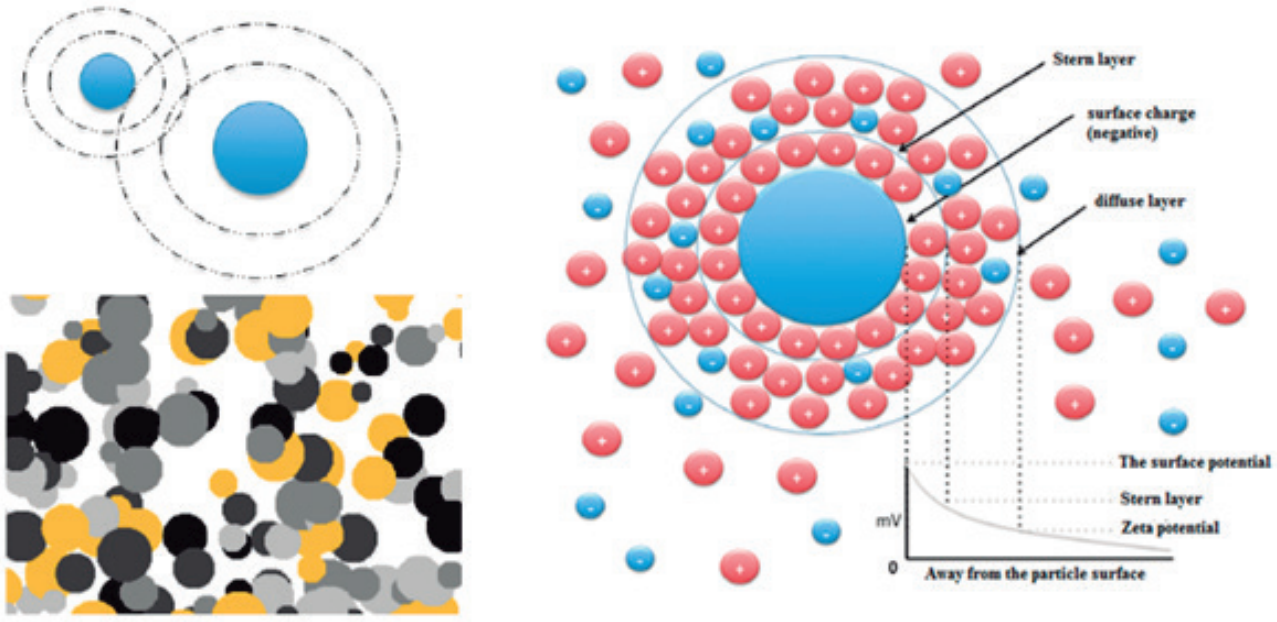


Figure 8 illustrates the sequence diagram, which represents operations and relations between classes. Following the stage of FDD "Design and Planning", you must define the database conceptual model.

We believe the main result of this study is a module in MASPN to manage experiments in laboratory. As it was previously explained, every simulation process needs a kind of validation (by mathematical or analytical models). Nevertheless, in the MASPN project the simulation will be validated using experimental data from different investigations stored in our system.

Figure 9 shows the validation process in the simulation. The parameters resulting from the characterization are inserted into the simulation environment that will assist in the simulation. The simulation will generate the animation of the particles and the repository of stored experiments will support the whole process. Therefore, the validation process occurs from the correlation of the parameters inserted in the simulation interface with the data stored in the environment database.

Figure 8 - Sequence Diagram for the interaction of operations.

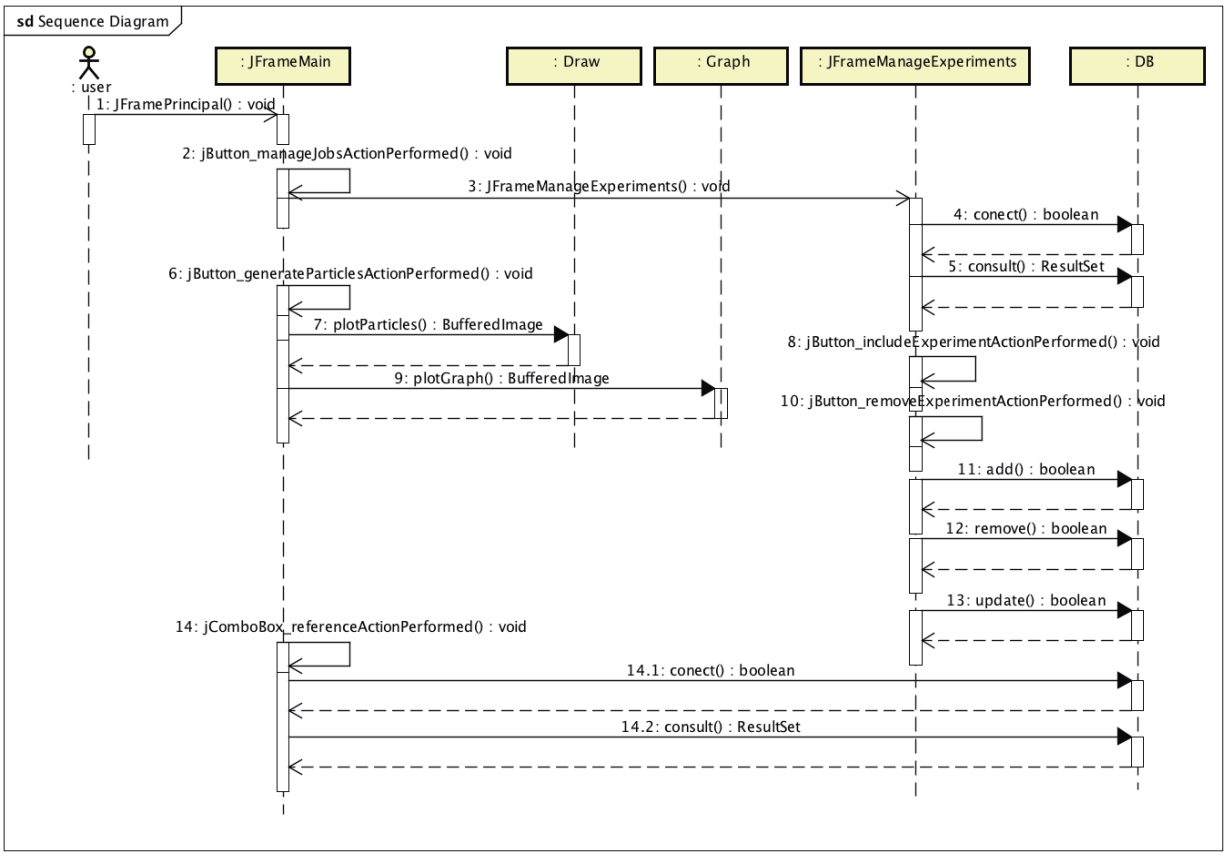
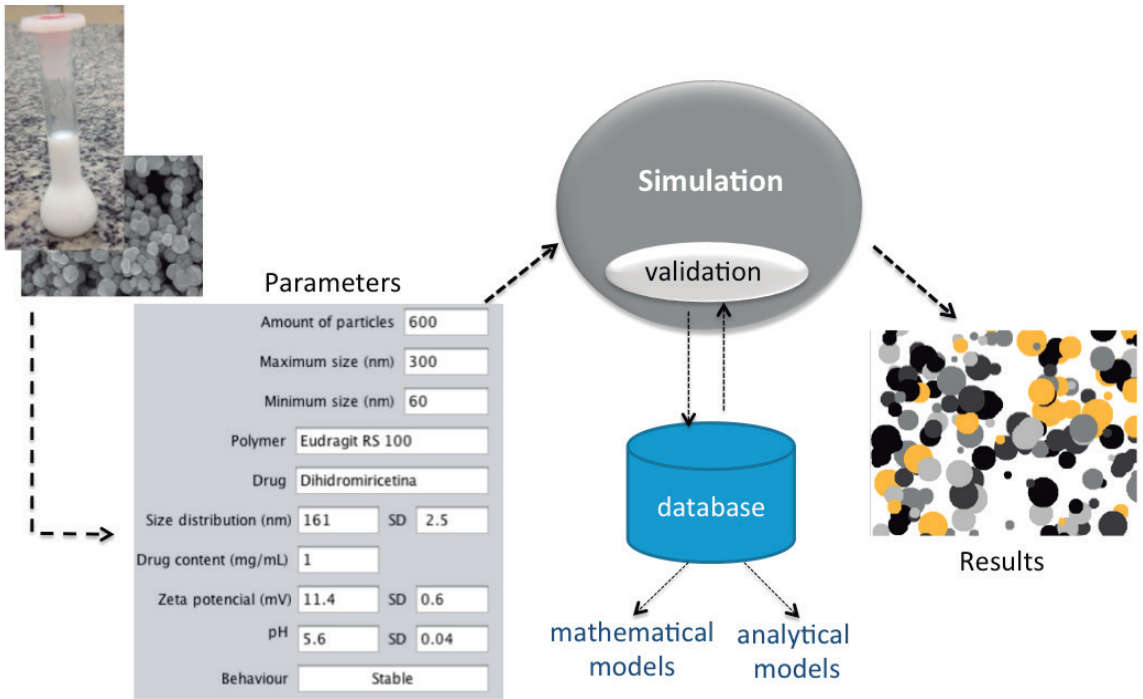


Figure 9 - Simulation environment and validation process by database.



CONCLUSIONS

The investigation has evaluated the physicochemical characteristics of polymeric nanoparticles and their agglomeration behaviour. In this way, a model was developed by the object-oriented analysis, in accordance with FDD methodology. The generated diagram represent functional and structural aspects of the environment MASPN, and present graphical interfaces.

As the modelling of the system is the main result of this paper, the use of models for validation is indicated for future work. About the MASP tool, there are features that need implementation, as the interaction among particles through multi-agent systems. At last, the significant results are the implementation of the features "Generate size distribution" and "Generate particle distribution".

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