IECP 2020
The 1st International Electronic Conference on Pharmaceutics
01–15 DECEMBER 2020 | ONLINE

Smart design nano-hybrid formulations by machine learning

Chaired by DR. ANDREA ERXLEBEN and PROF. DR. ELISABETTA GAVINI
pharmaceutics
MDPI

Raquel de Melo Barbosa[1*], Fabio Fonseca de Oliveira[2], Gabriel Bezerra Motta Câmara[1,2], Tulio Flavio Accioly de Lima e Moura[1], Fernanda Nervo Raffin[1], Marcelo Augusto Costa Fernandes[2,3]

[1]Laboratory of Drug Development, Department of Pharmacy, Department of Pharmacy, University of Rio Grande do Norte, Natal. Gal Gustavo C Farias street, s/n, Natal, 59078-970. Brazil.
[2]Laboratory of Machine Learning and Intelligent Instrumentation, IMD/nPITI, Federal University of Rio Grande do Norte, Natal 59078-970, Brazil.
[3]Department of Computer Engineering and Automation, Federal University of Rio Grande do Norte, Natal, RN 59078-970, Brazil.
*Correspondence: Raquel de Melo Barbosa. E-mail: m.g.barbosafernandes@gmail.com Tel.: +5584996124869

UFRN UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE

Laboratório de desenvolvimento de medicamentos

RESRC- LMLII

ABSTRACT: Nano-hybrid formulations combine organic and inorganic materials in self-assembled platforms for drug delivery. Laponite is a synthetic clay, biocompatible, and a guest of compounds. Poloxamines are amphiphilic four-armed compounds and have pH-sensitive and thermosensitive properties. The association of Laponite and Poloxamine can be used to improve attachment to drugs and to increase the solubility of β-Lapachone (β-Lap). β-Lap has antiviral, antiparasitic, antitumor, and anti-inflammatory properties. However, the low water solubility of β-Lap limits its clinical and medical applications. All samples were prepared by mixing Tetronic 1304 and LAP in a range of 1-20%(w/w) and 0-3%(w/w), respectively. The β-Lap solubility was analyzed by UV-vis spectrophotometry, and physical behavior was evaluated across a range of temperatures. The analysis of data consisted of response surface analysis (RMS), and two kinds of machine learning (ML): multilayer perceptron (MLP) and support vector machine (SVM). The ML techniques, generated from a training process based on experimental data, obtained the best correlation coefficient adjustment for drug solubility and adequate physical classifications of the systems. The SVM method presented the best fit results of β-Lap solubilization. *In silico* tools promoted a fine-tuning, and near experimental data show β-Lap solubility and classification of physical behavior to be an excellent strategy for use in developing new nano-hybrid platforms.

Keywords: Laponita RD; Tetronic T1304, response surface methodology; machine learning; thermoresponsive gels, drug solubilization.

IECP 2020

INTRODUCTION

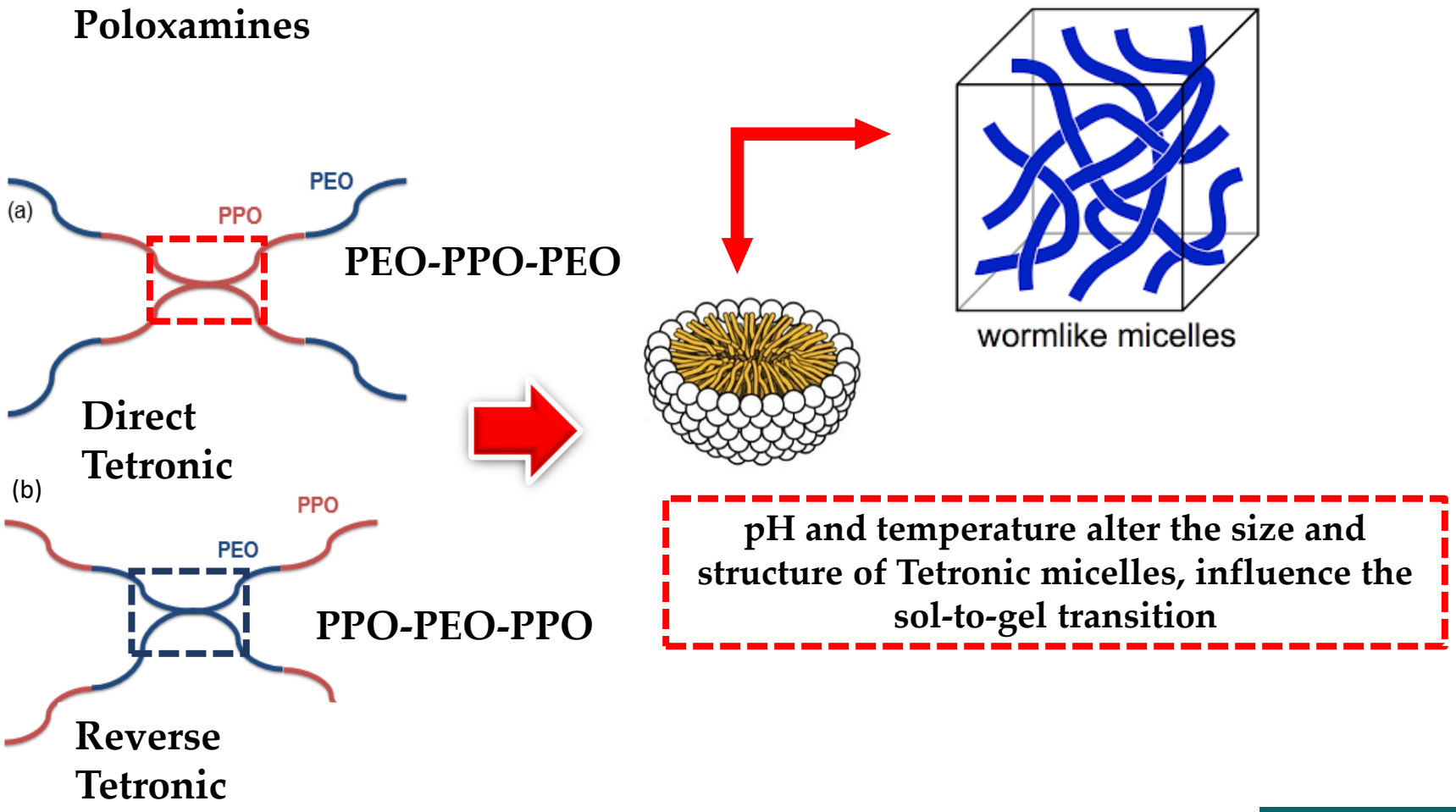


Figure 1: Schematic representation of Tetronic (a) direct and (b) reverse.

IECP 2020

INTRODUCTION

- A swelling nano-clay, composed of layered synthetic phyllosilicates with an octahedral MgO sheet sandwiched between two tetrahedral silica sheets;
- a chemical formula given by: $Si_8Mg_{5.4}5Li_{0.4}O_{24}Na_{0.7}$;
- widely used as a mechanical cross-linker to create hydrogels with robust mechanical properties;
- can also be used as a rheological modifier due to its ability to form gels when dispersed in polar solvents such as water.

Laponita® (Lap)

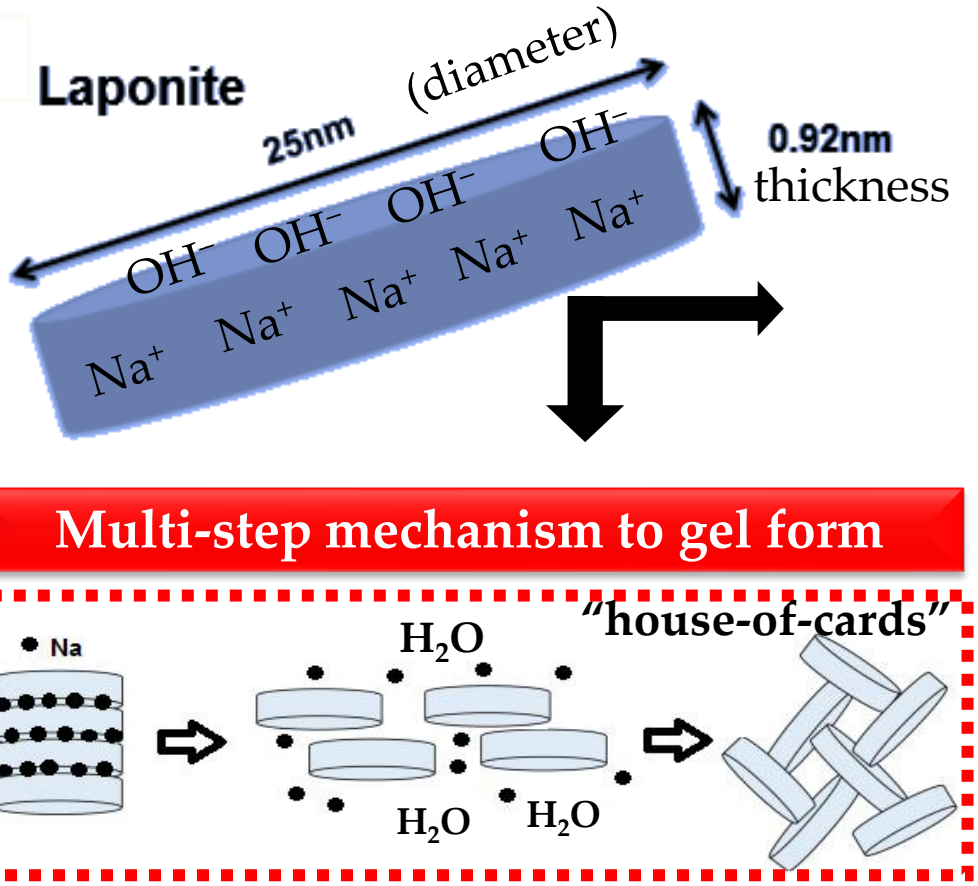


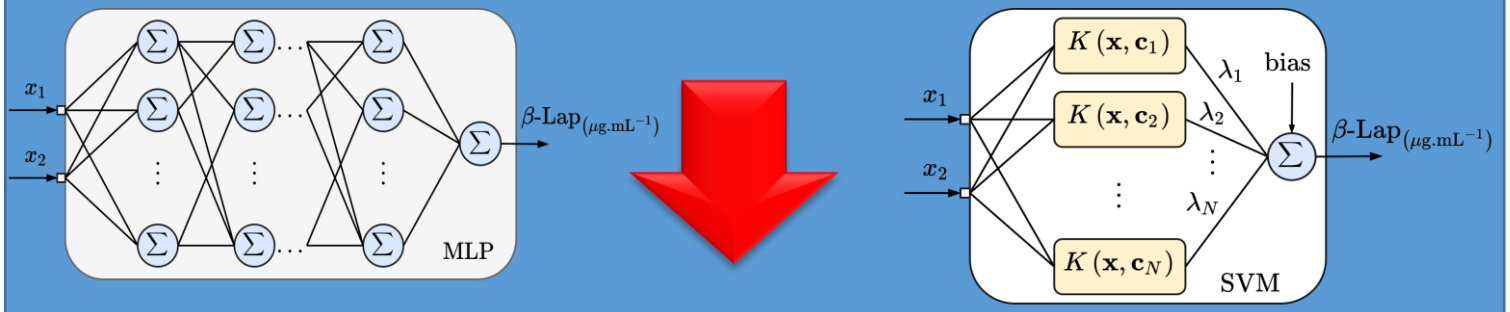
Figure 2: Schematic representation of the multi-step mechanism to gel forms from Laponite.

LAP interact with charged, polar, and nonpolar species. This interaction is due to its large charged surface, which enables the adsorption of ions or molecules through ion exchange, van der Waals forces, hydrogen bonding, and cation/water bridges, as well as protonation and ligand exchange at the edges of the crystal.

AIM

Develop multifunctional platforms to be used as nanotechnological systems, consisting of polymeric micelles prepared with the Tetronic® copolymer with or without the presence of LAP to deliver drugs with low water solubility.

Prepare and compared nano-hybrid formulation by physical behavior assays and their ability to increase the solubility of the β-Lap, a low solubility drug model.



Machine learning (MLP and SVM) and response surface analysis (RMS) to model the influence of the compounds used (T1304 and LAP) for the development of the nano-hybrid system.

ECP 2020

MATERIALS AND METHODS

Preparation of nano-hybrid

Tetronics (T1304)
(1, 5, 10, 15 e 20 %, w/w)

✚

Laponite
(0, 1.5 e 3.0 %, w/w)

Nanocomposites were prepared by adding LAP to water under constant stirring and adding Tetronic after 20 minutes and then leaving to stir for 24 hours. All samples were made in triplicates.

Characterization of the nano-hybrids

1. Quantification of βlap solubility

UV-Vis at 257 nm;
Dataset analysis by RSM, SVM and MLP.

2. Phase behavior

- Thermal bath in the range of 20-80 °C with 5 °C of step;
- Classification by SVM.

RESULTS

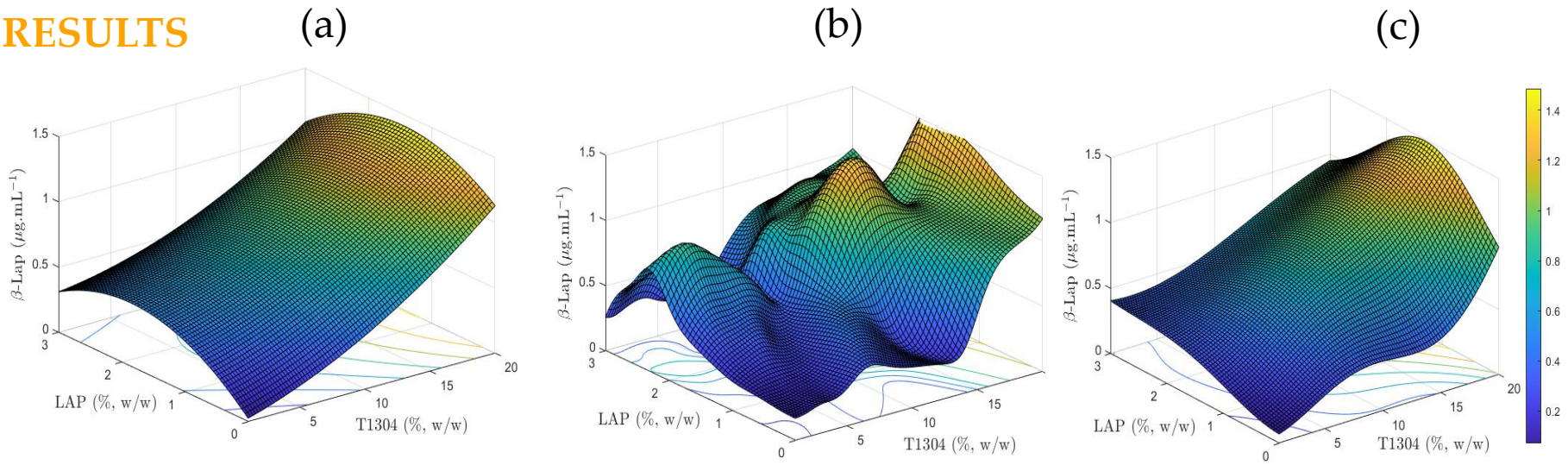


Figure 3: β-Lap solubility response surface: RSM (a), MLP (b), and SVM (c).

Table 1: The coefficients ($\beta_{1\text{-}5}$,) obtained from the RSM model.

Parameters	values	Parameters	values
β_0	-0.0005	β_{11}	0.0015
β_1	0.0262	β_{22}	-0.1345
β_2	0.5031	β_{12}	-0.0057

Table 2: Comparison between the techniques used.

Surface method	MSE		R^2	
	Fitting	Val.	Fitting	Val.
RSM	0.0105	0.0109	0.9279	0.9368
	Training	Val.	Training	Val.
MLP	0.0106	0.0098	0.9332	0.9433
SVM	0.0030	0.0045	0.9814	0.9737

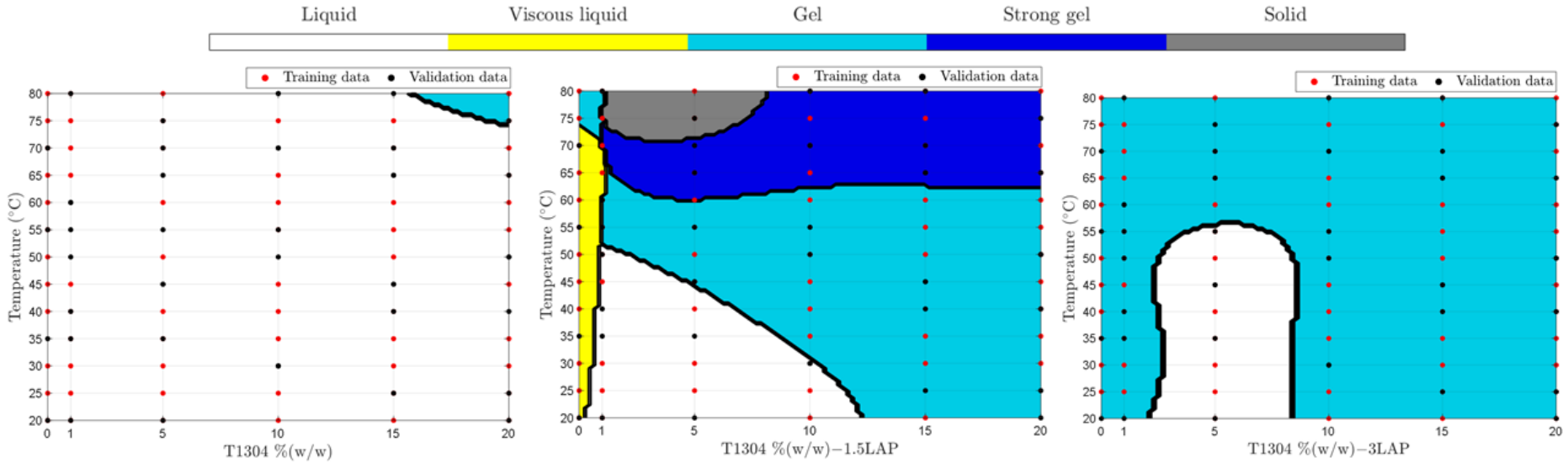


Figure 4: Phase behavior of different concentrations of T1304 and LAP from 20 to 80 °C ramp classified by SVM. The red dots are values used for ML training and the and black are values used for ML validation.

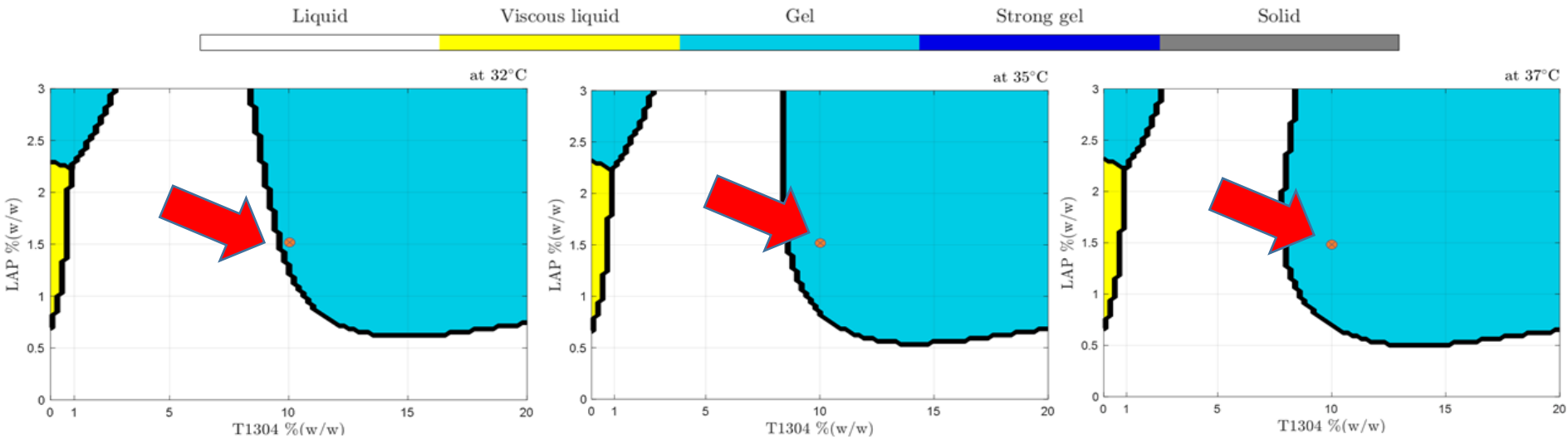
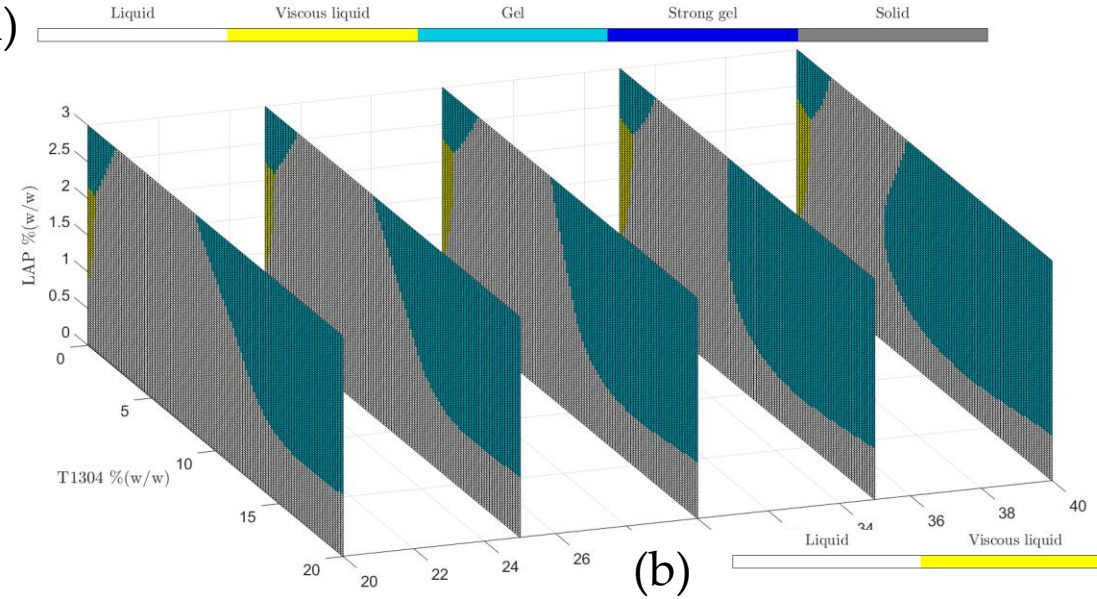


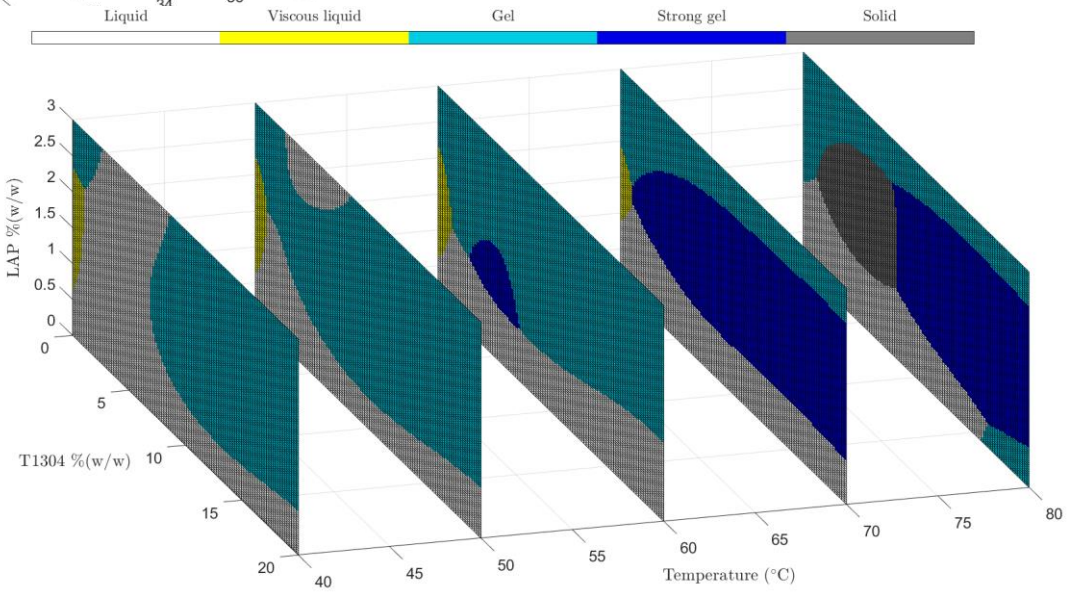
Figure 5: Phase behavior diagrams of different concentrations of T1304 and LAP classified by SVM at 32, 35 and 37°C (body temperatures in different parts such as skin, mouth and mucous membranes).

IECP 2020

(a)



(b)



- ✓ Prediction models based on machine learning techniques with an accurate response and high effectiveness have been increasingly used to develop pharmaceutical formulations.

- ✓ The purpose of using predictive techniques is to minimize costs (materials, equipment, workers, among others) and accelerate the development of new medicine with desire target characteristics..

Figure 6: Phase behavior diagrams of different concentrations of T1304 and LAP classified by SVM at ramp from 20 ºC to 40 ºC (a) and from 40 oC to 80 ºC (b).

IECP 2020

CONCLUSIONS

- ✓ The association of Tetronic and Laponite in different concentrations allowed the formation of systems that present different phase behaviors as a function of temperature.

- ✓ LAP have a great influence in the liquid-gel transition of the systems. β-Lap solubility have expressive increase in samples T1304 (over 10%) and 1.5% LAP, or systems with only LAP (1.5%).

- ✓ *In silico* tools promoted a fine-tuning and near experimental data shown to be an excellent strategy for use in the development of news nano-hybrid platforms

ACKNOWLEDGMENTS

Organizing of Congress

Institutions

UFRN

EX SEMINE SEGES
UFRPE

Companies

BYK
Additives & Instruments

BASF
We create chemistry

FUNDING:

This research was financially supported by CAPES [1975/2015] and CAPES [1777580].