MODELLING OF NANOCAPSULES FORMATION: PHASE SEPARATION DURING MASS TRANSFER PROCESSES

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1. Introduction

This paper presents an improved approach in the modelling of phase equilibria based on the global optimization of the free energy and phase stability analysis. In this method, genetic algorithms coupled with a local method of optimization, a general objective function with finite-difference gradient are used to calculate phase's equilibrium.

This method can be summarized in two stages:

- Initially all global minima are searched by direct minimization of free Gibbs energy (G). The objective function is the sum of the absolute values of the first derivative of G. Afterwards the result is automatically integrated in the second subroutine of minimization to check the equality of chemicals potentials. This allows to locate the zone of all coexisting phases (maximum three in our case). In this latter zone, the mixture will be separated into three phases. Outside of this zone, one or two phases are present.
- Next the tangent plane distance function (TPDF) is used to test system stability outside this zone. When the system is unstable, the minimization of (TPDF) gives good initial estimates for the second subroutine of minimization.

The proposed model is capable to predict precisely the phase stability. In the case of instability, the model gives the exact number of phases. Results on phase equilibrium problems show that this model is reliable to find minima in all the cases that have been tested.

Later this model will be coupled with the Stefan-Maxwell model to describe the mass transfer process during the nanocapsule formation.

2. Nanocapsules formation

2.1. Nanocapsules

Nanocapsules are synthetic colloidal systems ranging in size from 10 to 500nm, consisted of a core in which an active ingredient can built-in, and surrounded by a thin membrane of polymer (Fig 1)

Nanocapsules have received considerable attention in recent years, in particular those prepared with biodegradable polymers, because of their potential use as site-specific drug delivery systems [1].

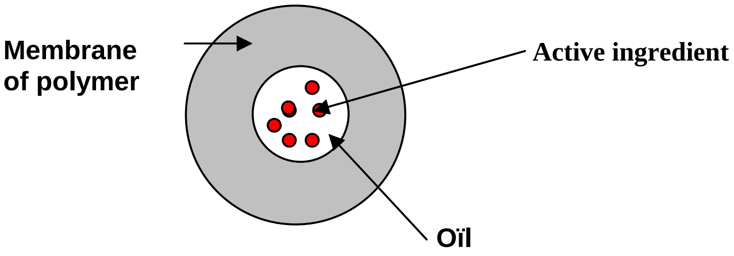


Figure 1 nanocapsule formation

The formation of nanocapsule is called encapsulation. Encapsulation allows to enhance the drug stability by protecting the active agent from its environment and by reducing adverse or toxic effects. Another objective of these delivery systems is to control the further release of the drug. The main interest of these colloidal vectors is to enhance the therapeutic effect by targeting the active molecule to its site of action and by creating a high local concentration.

2.2. Materials and method

2.2.1. Materials

The polymer used for the nanocapsules formation is poly-E-caprolactone PCL (Sigma Aldrich Chemica Company Inc., USA). Its average molecular weight (Mw) was given by the supplier as close to 80,000 D.
The oil was labrafac lipophilic WL 1349, a mixture of triglycerides of fatty acids caprylic (C8)/capric (C10) from gattefossé. The solvent is the pure ethyl acetate from Laurylab.
The stabilizer is polyvinyl alcohol (Mowiols 40-88, 88% hydrolyzed, Mwca 127,000 D from Aldrich Chemical Company).
Distilled water saturated with solvent is used as a non-solvent and distilled water as a diluent for the emulsion.

2.2.2. Method

The method proposed to prepare nanocapsules in this study is the emulsification–diffusion. The original of this technique is due to Quintanar-Guerrero [1996] [2]; this process involves the emulsification of a partially water-miscible solvent (previously saturated with water), containing the polymer and oil, in an aqueous phase (previously saturated with the solvent), containing a stabilizer. The subsequent addition of large volume of water to the system causes the solvent to diffuse into the external phase, causing the polymer's deposition around the droplets, then the formation of nanocapsules **(**Fig 2**)**.

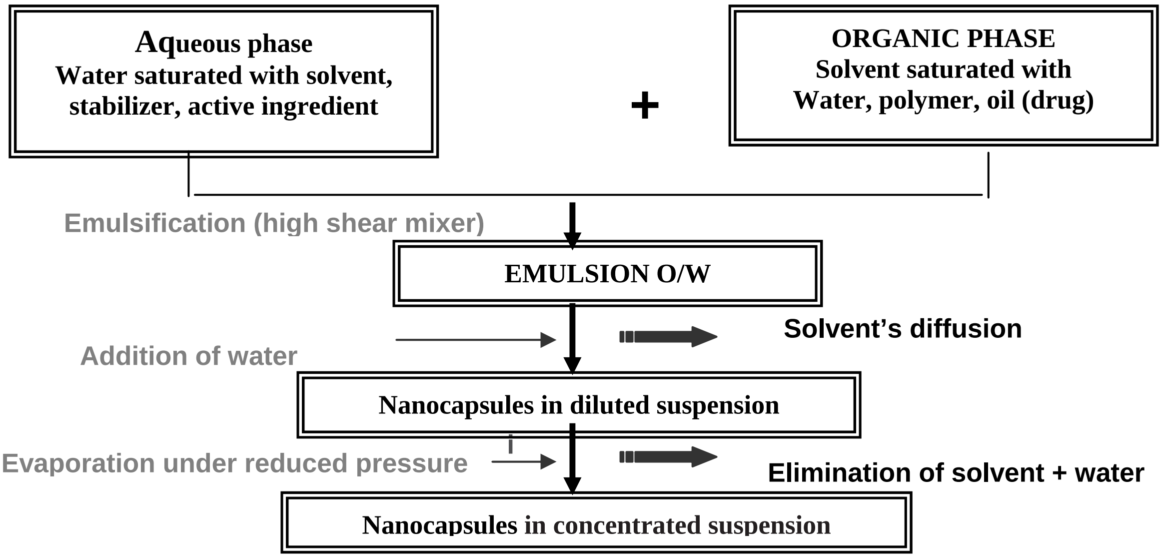


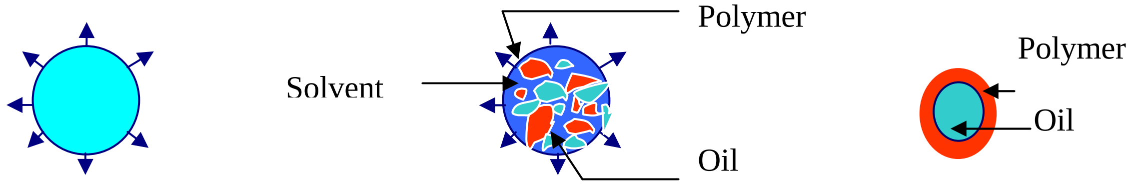
Figure 2 Preparation of Nanocapsules by emulsion diffusion method

3. **Model description**

The nanocapsule formation is controlled by two phenomena: the phase separation and the mass transfer and, thus by the competing kinetics between those two phenomena. Indeed the dilution causes the diffusion of the solvent from the droplets towards the continuous phase and shifts the mixture composition inside the droplets. Thus we have the phases separation inside the droplets and the formation of the distinct nano-phases (polymer-rich phase, solvent rich phase and oil rich- phase) (Fig 3). At the same time the solvent concentration inside the droplet decreases because of the diffusion and the size of nanocapsule decreases.

The following assumptions were made in the model**:**

- There are two systems, the external one which represents the exterior of the nanocapsule {solvent + non-solvent} and the internal one {solvent-water + polymer + oil}
- Only three components are inside the nanocapsule (solvent, polymer, oil). The solvent saturated with water has the same behaviour that the solvent alone.
- Nanocapsules are represented by symmetrical spheres
- Diffusion according to r (radius)
- The energy of the mixture inside the nanocapsules is described by the Flory-Huggins thermodynamic model
- All the components inside the volume dV are in equilibrium.



Solvent Diffusion Phase's Separation Formation of Nanocapsule

Figure 3 : Phase separation during mass transfer processes

In this paper, only the thermodynamic model which describes the process of phases separation into the nanocapsule is presented.

3.1. Thermodynamic model

The Gibbs free energy of mixing is given by the Flory–Huggins functional [3], thus for a ternary system we have:

$$\Delta G_M = RT(n_1 \ln(\phi_1) + n_2 \ln(\phi_2) + n_3 \ln(\phi_3) + \chi_{12} n_1 \phi_2 + \chi_{13} n_1 \phi_3 + \chi_{23} n_2 \phi_3 \qquad (1)$$

Where n_i is the mole number of component i; Φ_i, the volume fraction of component i; R, the ideal gas constant; and T, the absolute temperature. The subscripts refer to nonsolvent (1), solvent (2), and polymer (3), respectively.
χ_{13} is the nonsolvent-polymer interaction parameter, and χ_{23}, the solvent-polymer interaction parameter and χ_{23} is the nonsolvent-solvent interaction parameter.

We suppose that

$$\phi_i = x_i \qquad (2)$$

Or

$$n_i = n_{tot} x_i \tag{3}$$

Were x_i is the mole fraction of species i, and n_{tot} is the number of moles of mixture.

Then $$\Delta G_M = n_{tot} RT (x_1 \ln(x_1) + x_2 \ln(x_2) + x_3 \ln(x_3) + \chi_{12} x_1 x_2 + \chi_{13} x_1 x_3 + \chi_{23} x_2 x_3) \tag{4}$$

With $$x_1 + x_2 + x_3 = 1 \tag{5}$$

Hence G can be written as a function of x_1 and x_2 only

$$\frac{\Delta G_M}{n_{tot} RT} = x_1 \ln(x_1) + x_2 \ln(x_2) + (1 - x_1 - x_2)\ln(1 - x_1 - x_2) + \chi_{12} x_1 x_2 + \chi_{13} x_1 (1 - x_1 - x_2) + \chi_{23} x_2 (1 - x_1 - x_2) \tag{6}$$

$$g = x_1 \ln(x_1) + x_2 \ln(x_2) + (1 - x_1 - x_2)\ln(1 - x_1 - x_2) + \chi_{12} x_1 x_2 + \chi_{13} x_1 (1 - x_1 - x_2) + \chi_{23} x_2 (1 - x_1 - x_2) \tag{7}$$

With $$g = \frac{\Delta G_M}{n_{tot} RT} \tag{8}$$

The chemical potential μ_i of each component was calculated from the first derivative of the expression given by (Eq 4) with respect to composition.

$$\frac{\Delta \mu_i}{RT} = \frac{\partial}{\partial n_i} \left(\frac{\Delta G_M}{RT} \right)_{n_j, j \neq i} \tag{9}$$

$$\mu_i = g + (1 - x_i) \left(\frac{\partial g}{\partial x_i} \right)_{T,P,x_{K \neq i}} - \sum_{j=1, j \neq i}^{C-1} x_j \left(\frac{\partial g}{\partial x_j} \right)_{T,P,z_{K \neq j}, x_j \neq x_i} \tag{10}$$

3.1.1. Problem formulation

The problem of locating the equilibrium compositions of a multi-component system at a temperature T and a pressure P can be formulated as a minimization problem as the true solution for mixtures corresponding to the global minimum Gibbs free energy.

So there are three restrictions that all phase equilibrium solutions must satisfy [4]

- The material balance must be preserved.
- The chemical potentials for each component must be the same in all the phases.
- The system of predicted phases at the equilibrium state must have the lowest possible Gibbs energy at the system temperature and pressure.

This problem can be described mathematically as follows:

$$\begin{gathered} \min G_M \\ with \quad \sum_{\phi=1}^{\Pi} n_i^{\phi} = n_i \\ \sum_{i=1}^{C} n_i = n_{tot} \\ with \;\; i = 1, \dots, C-1 \end{gathered} \tag{11}$$

Were G_M is the Gibbs free energy, μ_i^α the chemical potential of component i in the phase α, n_i the number total of moles of the component i, n_i^Φ the number total of moles of the component i in the phase Φ, Π the number of the coexisting phases, C the number of the components, n_{tot} the number total of moles, respectively.

According to Eqs (11), Π-1 equations are to be satisfied for each component i during the minimization the free energy of mixing G. So that means finding the tangent plane equations for the Gibbs energy function.

3.1.2. The computation procedure

3.1.2. 1.First stage

At first all the stationary points are searched by direct minimization of the function g. In these points the partial derivatives of the g with respect to x_1 and x_2 (at constant temperature and pressure) become zero and the determinant of the matrix of the second-order partial derivatives of g with respect to the mole fraction at the same conditions should be positive definite:

$$\frac{\partial g}{\partial x_1} = 0 \qquad (12)$$

$$\frac{\partial g}{\partial x_2} = 0 \qquad (13)$$

And

$$\begin{vmatrix} \frac{\partial^2 g}{\partial {x_1}^2} & \frac{\partial^2 g}{\partial x_1 \partial x_2} \\ \frac{\partial^2 g}{\partial x_1 \partial x_2} & \frac{\partial^2 g}{\partial {x_2}^2} \end{vmatrix} > 0 \qquad (14)$$

To locate these points, an optimization technique based on the successive use of a genetic algorithm (GA) is used, this algorithm will be presented in next section. The objective function f_1 in this case is the sum of the absolute values of the first derivative of g.

$$f_1 = abs\left(\frac{\partial g}{\partial x_1}\right) + abs\left(\frac{\partial g}{\partial x_2}\right) \qquad (15)$$

This function would be positive or null; the minimum in this case is zero.

So if f1 = 0 then $\frac{\partial g}{\partial x_1} = 0$ and $\frac{\partial g}{\partial x_2} = 0$. Thus the system (14), can be satisfied by minimizing f_1. In this case all the minima have the value equal to zero.

Afterwards the determinant of the Hessian at the saddle points is calculated. If the Hessian is positive definite at these points, they are minima, so they are saved. Else if it is negative definite, they are rejected.

To improve the reliability of locating all minima, this algorithm is repeated several times to allow exploring all search space.

Next the final results are automatically integrated in the (LCONF) subroutine (this routine is available in the IMSL Library (visual numeric)) to check the chemical potentials equality. The objective function f_2 to minimize in this case is:

$$f_2 = \sum_{i=1}^{C-1}\left[\sum_{J=1}^{2} abs\left(\mu_i^J - \mu_i^{j+1}\right)\right] \qquad (16)$$

Constraints: $$\sum_{i=1}^{C} x^{j}{}_{i} = 1 \qquad 0 \le x^{j}{}_{i} \le 1 \tag{17}$$

3.1.2. 2.Second stage

In this step, a preliminary test of stability based on Gibbs' tangent plane criterion established by Backer et al.(1981) and Michelson (1982a, b) is applied[5] [6] [7].

Let z be the overall composition (at a temperature T and a pressure P), a necessary and sufficient condition for an equilibrium postulated solution is that the tangent plane distance function, denoted by:

$$D(x) = \sum_{i=1}^{Nc} x_i * (\mu_i(x) - \mu_i(x)) \tag{18}$$

must be non negative for all possible phases in the system. The tangent plane distance function is defined as the distance between the Gibbs surface and the tangent plane associated with this surface at z.

Where *N*c is the number of the components, and μ_i represents the chemical potential of component i respectively.

A common approach for determining if D(x) is negative for all x, is to minimize D(x) with the constraints

$$\sum_{i=1}^{C} x_i = 1 \quad and \quad 0 \le x_i \le 1 \tag{19}$$

The method suggested here for minimization is the genetic algorithm, the same code as in the first stage is used.

So if D(x) is positive for all range of x, then the postulated solution corresponds to the global minimum of the Gibbs free energy and the system is stable with one phase. If not, it will be separated in two phases with lower Gibbs free energy.

In this stage, the composition that minimizes D(x), corresponds to a first stationary point. Then this point is used to find the second stationary point. The barycentre z' of the point z and the previously found stationary point is calculated. D'(x), the distance between the Gibbs surface and the tangent plane associated with this surface at z' is minimized. The result here is the second stationary point of D(x).

Finally the result is injected into the second subroutine to check the equality of chemicals potentials for each component into the two phases.

The objective function here is: $$f_3 = \sum_{i=1}^{C-1} \left[abs\left(\mu_i^{j} - \mu_i^{j+1} \right) \right] \tag{20}$$

Constraints $$\sum_{i=1}^{C} x^{j}{}_{i} = 1 \qquad 0 \le x^{j}{}_{i} \le 1 \tag{21}$$

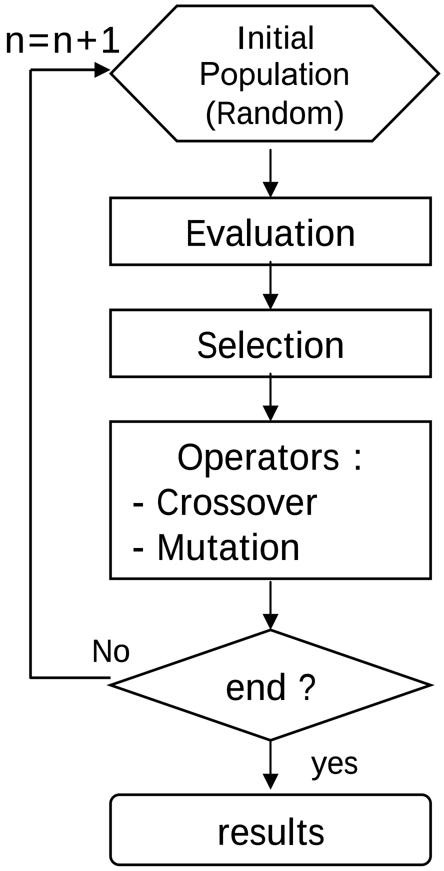
4. The global optimization method

Genetic algorithms (GA) are a stochastic global optimization technique that simulates natural evolution on the solution space of the optimization problems. It originated from the studies of cellular automata, conducted by John Holland and his colleagues at the University of Michigan [8] [9].

GA is typically implemented as a computer simulation in which a population of abstract representations (called *chromosomes*) of candidate solutions (called *individuals*) of an optimization problem evolves toward better solutions. Traditionally, solutions are represented in binary as strings of 0s and 1s, but different encodings are also possible. The evolution starts from a population of completely random individuals and happens in generations. In each generation, the fitness of the whole population is evaluated, multiple individuals are stochastically selected from the current population (based on their fitness), modified (mutated or recombined) to form a new population, which becomes current in the next iteration of the algorithm.

- Genetic algorithm procedure

The genetic algorithm procedure can be summarized as follows:



5. Application of the method

To test this method, four examples of ternary mixture with one, two and tree phases in equilibrium are selected. Only one example is represented.

For this example the energy of mixing is written as follows

$$g = x_1 \ln(x_1) + x_2 \ln(x_2) + (1 - x_1 - x_2)\ln(1 - x_1 - x_2) + \chi_{12} x_1 x_2 + \chi_{13} x_1 (1 - x_1 - x_2) + \chi_{23} x_2 (1 - x_1 - x_2)$$

Where $X_{12} = 2.814$, $X_{23} = 2.8$ and $X_{13} = 2.852$

The Gibbs free energy surface in this case is represented in figure 4 and its projection in figure 5

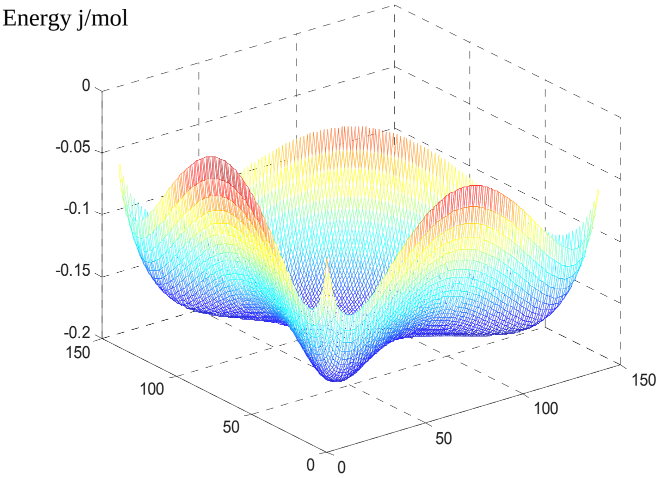


Fig 4 Gibbs free energy surface

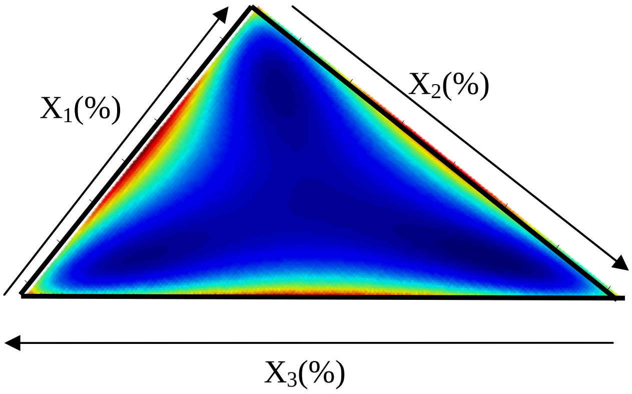


Fig 5 Gibbs free energy surface projection

Fig 4 and Fig 5 show that the Gibbs free energy function has three global minima and several local minima. The methodology described before is used here to calculate phases Equilibria.

Initially the method described in paragraph 3.1.2.1is applied to determine the global minima. The results are summarized in table 1, they represent three phases in equilibrium.

Table 1 global minima

	Phase I	Phase II	Phase III
x_1	0.1414	0.7097	0.1182
x_2	0.1508	0.1255	0.7040
x_3	0.7078	0.1648	0.1778

Previous results allow writing the equations that delimit the zone where the three phases coexists:

$$\left.\begin{array}{l} x_2 + 0.045x_1 - 0.16 > 0 \\ x_2 + 23.84x_1 - 3.52 > 0 \\ x_2 + 0.98x_1 - 0.81 < 0 \end{array}\right\} Z(x)$$

Geometrically Z(x) represents a triangle where three phases coexists. Outside of this zone one or two phases are possible.

Simulations results outside this zone are represented in table 2, method described in paragraph 3.1.2.21is used here.

Table 2 calculations oh phases Equilibria outside Z(x)

Feed composition	Stability	News phases compositions
X_1=0.1 X_2=O.1	stable	X_1=0.1 X_2=0.1
X_1=0.1 X_2=O.2	unstable	X^I_1=0.087 X^{II}_1=0.086 X^I_2=0.793 X^{II}_2=0.108
X_1=0.3 X_2=O.1	unstable	X^I_1=0.858 X^{II}_1=0.085 X^I_2=0.042 X^{II}_2=0.06
X_1=0.8 X_2=O.1	stable	X_1=0.8 X_2=0.1
X_1=0.5 X_2=O.1	unstable	X^I_1=0.107 X^{II}_1=0.865 X^I_2=0.069 X^{II}_2=0.052
X_1=0.1 X_2=O.5	unstable	X^I_1=0.077 X^{II}_1=0.053 X^I_2=0.116 X^{II}_2=0.859
X_1=0.1 X_2=O.6	unstable	X^I_1=0.056 X^{II}_1=0.050 X^I_2=0.107 X^{II}_2=0.861

6. Conclusion and perspectives

In this paper we advocate improved approach in the modelling of phases Equilibria.
The developed method exploits two techniques of optimization: genetic algorithms and local method of optimization, a general objective function with finite-difference gradient.

A method for locating the local minima based in the minimization of (TDPF) is presented. So the minimization of (TDPF) gives us the first stationary point. Then this point is used to find the second stationary point. The barycentre z' of the point z which represents the feed composition and the previously found stationary point is calculated. D'(x), the distance between the Gibbs surface and the tangent plane associated with this surface at z' is minimized. The result here is the second stationary point of D(x).

This method proved to be capable to predict precisely the phase stability for ternary system.

In addition, the future developments of the model will include mass transfer to describe the nanocapsule formation.

Notations

f	objective function
G	Gibbs free energy
Ni	mol number of component i in feed
C	number of components
R	universal gas constant
T	temperature
$\mu_i(x)$	the chemical potential of component i at x,

$\mu_i(z)$	the chemical potential of component *i* at *z*,
$D(x)$	the tangent plane distance function.
x_i	the mole fraction of species i
χ_{13}	the nonsolvent-polymer interaction parameter
χ_{23}	the solvent-polymer interaction parameter
χ_{23}	the nonsolvent-solvent interaction parameter
μ_i^{α}	the chemical potential of component i in the phase α
n_i^{Φ}	the number total of moles of the component i in the phase Φ
Π	the number oh the phases coexists
n_{tot}	the number total of moles
j	denote phases

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