

Modeling of Controlled Release of Betacarotene Microcapsules in Ethyl Acetate

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Abstract: In this work several models of mass transfer process were used for modelling and simulating active principles release of polymeric microcapsules of the matrix type. To demonstrate the performance of each model compared to the experimental data, a statistical analysis using the F test was done. The following mathematical models were used on this mass transfer problem: 2^a. Law of Fick (CDMASSA), LDF - Linear Drive Force, analytical model and others semiempirical models. The results obtained were compared with those available in the literature. In this work the release of the active ingredient betacarotene, contained in microcapsules (PHBV) in the solvent ethyl acetate, was studied. It was observed that the model obtained from the 2^a. Law of Fick fits better on the literature data compared to the models: LDF, analytical and semiempirical. The most complete model, based on the phenomenology of the problem, provide a better result, considering that it was able to represent the fundamental stages of the mass transfer process, such as the resistance to mass transfer on the microcapsule surface, where the numerical results were very close to the experimental results.

Keywords: Release, Microcapsules, Modeling, Active Principles, Simulation

1. Introduction

Always a polymeric structure is produced for the encapsulation and release of active substances, there is a need to predict how these systems would behave in relation to the release of these components into the respective fluid medium. It is necessary to ensure the release of a suitable form of an active principle, as well as to predict how the release would take place over time, to ensure the efficiency and even safety into the medium [1].

A good prediction of the microencapsulated active compounds release depends fundamentally on a phenomenological numerical model suitable for these systems. This resolution models should predict the behavior of the release by changing the resistance between phases, interaction of substances at interfaces, swelling, variation of

pore distribution and connection with the external medium, among others [2].

Controlled release technologies are being used to provide compounds, such as drugs, pesticides and fragrances at established rates, improving the efficient, safer, and consumer-friendly action [3–6].

When a drug is given as a pill, its concentration increase abruptly and shortly after ingested [7]. This increase may lead to drug concentration beyond the effective level and shortly above the toxic level. The concentration then falls below the effective level. In contrast, when the drug is administered by controlled release, its concentration remain on the required level to be effective, avoiding abrupt fluctuations of toxic concentrations or ineffective levels.

In this work the release of microencapsulated betacarotene in poly-(3-hydroxybutyrate-co-3-hydroxyvalerate) PHBV is studied, being this a natural polyester obtained from

microorganisms [8].

2. Materials and Methods

2.1. Materials

The studied nanospheres were prepared from a PHBV with molar mass of 196.000 and polydispersity index of 1.85 (measured by GPC using a calibration curve obtained from polystyrene standards), was kindly supplied by the PHB Industrial S. A. (Brazil). The solvent ethyl acetate from Merck (Germany), with purity greater than 99.0%, was used as received. The preparation procedure and characterization of nanospheres were described in [8]. Four types of nanoparticles of varying drug content with same size, the mean diameter size particle was about 5.50×10^{-5} cm. The drug loadings varied from β -Carotene mass fraction 28 to 49 % (w/w).

2.2. β -Carotene Release in Vitro

To determine the β -carotene release kinetics in the organic solvent, the system temperature and orbital motion were kept constant at 313.15 ± 0.5 K and 80 rpm, respectively. For the release experiments, four β -carotene concentrations into organic solution varying from 12 to 30 mg mL⁻¹, at a fixed PHBV concentration of 30mg mL⁻¹. All tests were performed in 100 mL Erlenmeyers flasks, protected at the top with plastic wrap to prevent solvent evaporation, incubated in an air-bath orbital shaker (Nova Etica, model 501/1D) with temperature controlled within 1 K. At scheduled time intervals, 2.0 mL was collected from the solution and immediately replenished with pure solvent to maintain the original volume.

2.3. Mathematical Modeling

In the engineering view, the numerical tool is adequate and reliable when one is in possession of a numerical method that correctly solves the differential equations, and of a mathematical model that, knowingly, represents with fidelity the physical phenomenon [9–11].

The mathematical modeling utilizing in this work presents four types of analysis: release modeling of the active agent dispersed in a polymer matrix, where the diffusion coefficient and the mass transfer coefficient are the main parameters of the mass transfer process; The modeling of a solid matrix with the dispersed active agent, which dissolves over time, without altering the volume; The use of semi-empirical models for the release of active principles and the use of the analytical model for 2^a. Law of Fick.

Modeling a Matrix where the diffusion coefficient and the mass transfer coefficient are the main parameters of the mass transfer process

In this model, we have a sphere, with the hypothesis that there is no changing in the volume of the same, in a stirred bath at constant temperature. The active substance diffuses to the surface microcapsule and encounters a external resistance to the mass transfer. There are situations in which the

external environment (medium 2) influences what happens in the medium 1. When considering this influence, an associated resistance is assumed, different from that of medium 1 [3] (Figure 1). For the elaboration of the model, the following hypotheses are considered:

- (1) Microcapsule of matrix type;
- (2) There is no concentration gradient inside the agitated reactor (medium 2);
- (3) Transient regime: there is variation of concentration with time in the medium 1 and 2;
- (4) Temperature, pressure and constant stirring;
- (5) The particle is modeled as a sphere;
- (6) The mass transfer flow is unidimensional in radial direction;
- (7) Resistance to mass transfer within the particle (D_{pol}^{-1}) is adjusted to the experimental model;
- (8) External resistance to mass transfer, related to the coefficient k_{m2} ;
- (9) There is no chemical reaction.

For the calculation of the D_{AB} , will be used a correlation based on the Stokes-Einstein relation, which is known as the Wilke-Chang equation [12]:

$$D_{AB} = \frac{7,4 \times 10^{-8} (\phi M_B)^{1/2} T}{\mu_B V_{bA}^{0,6}} \quad (1)$$

Where T is the temperature, μ_B is the dynamic molecular viscosity of the medium, M_B is the molecular weight of B, V_b is the molar volume at the normal boiling temperature and ϕ is the solvent-associated parameter; $\phi = 2.6$ (water), $\phi = 1.9$ (methanol), $\phi = 1.5$ (ethanol) and $\phi = 1$ (solvents remainder).

The k_{m2} can be calculated by equation (2), and is correlated with the number of Sherwood [13], given by:

$$k_{m2} = \frac{D_{AB}}{R_p} (1 + 0,3Re^{0,5}Sc^{0,33}) \quad (2)$$

Where Re is the Reynolds number and Sc is the Schmidt number.

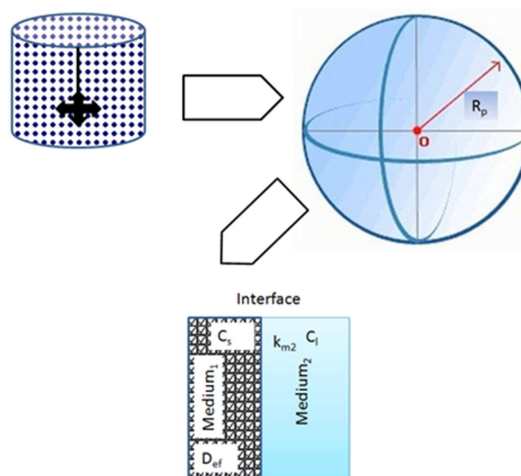


Figure 1. Schematic modeling represents the matrix with external resistance to mass transfer.

The D_{AB} is calculated with respect to the molar fraction

through the equations:

$$D_{AB} = D_{ABWC} \left[1 + x_A \frac{\partial \ln \gamma_A}{\partial x_A} \right] \quad (3)$$

$$\ln \gamma_A = V_A \Phi_B^2 (\delta_A - \delta_B)^2 \quad (4)$$

$$\Phi_B = \frac{x_B V_B}{x_A V_A + x_B V_B} \quad (5)$$

$$D_{AB} = D_{ABWC} \left[1 + x_A \left(-\frac{2(\delta_A - \delta_B)^2 V_A (V_A - V_B) V_B^2 (1 - x_A)^2}{RT (V_B (1 - x_A) + V_A x_A)^3} - \frac{2(\delta_A - \delta_B)^2 V_A V_B^2 (1 - x_A)}{RT (V_B (1 - x_A) + V_A x_A)^2} \right) \right] \quad (6)$$

2.3.1. Mass Balance in Solid Phase

The balance of active principle i (for example, beta-carotene) will be performed in the control volume defined as a sphere of radius R_p (Figure 2).

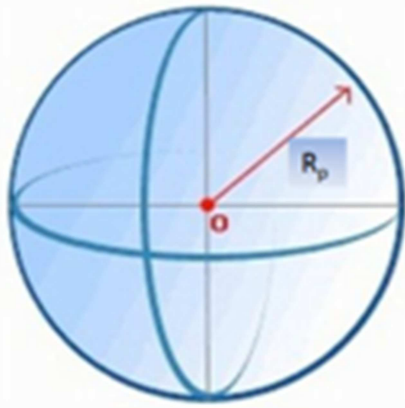


Figure 2. Scheme of the modeling made of the microsphere.

The conservation equation of the chemical species A in terms of mass, in spherical coordinates, adopting the hypotheses previously assumed, is given by:

$$\frac{\partial C_A}{\partial t} = D_{pol} \left[\frac{\partial^2 C_A}{\partial r^2} + \frac{2}{r} \frac{\partial C_A}{\partial r} \right] \quad (7)$$

Equation 7 is also known as 2^a. Law of Fick and this is the equation that will be solved computationally for the solid phase in this work. The boundary conditions for the problem are as follows:

Initial conditions.

$t = 0$; $0 \leq r \leq R_p$, $C_A = C_{Ai}$; (to any point within the sphere at the initial time the concentration is the initial concentration of the active ingredient).

Boundary conditions.

$t > 0$; $r = 0$, applying the limit with r tending to zero in Equation 7 is defined as:

$$\lim_{r \rightarrow 0} \left(\frac{\partial C_A}{\partial t} \right) = D_{pol} \left[\lim_{r \rightarrow 0} \left(\frac{\partial^2 C_A}{\partial r^2} \right) + \lim_{r \rightarrow 0} \left(\frac{2}{r} \frac{\partial C_A}{\partial r} \right) \right] \quad (8)$$

Applying L ^ Hôpital on the second term on the right side, we obtain:

$$\lim_{r \rightarrow 0} \left(\frac{\partial C_A}{\partial t} \right) = D_{pol} \left[\lim_{r \rightarrow 0} \left(\frac{\partial^2 C_A}{\partial r^2} \right) + 2 \lim_{r \rightarrow 0} \left(\frac{\frac{\partial^2 C_A}{\partial r^2}}{1} \right) \right] \quad (9)$$

The D_{ABWC} diffusivity is obtained by the Wilke Chang correction, V is the molecular volume of A or B compounds and δ is the solubility of compounds A or B. Using the commercial computer program Mathematica 4. These relationships are resolved by the next analytical equation:

Therefore, the equation can be rewritten as follows:

$$\frac{\partial C_A}{\partial t} = 3D_{pol} \left[\frac{\partial^2 C_A}{\partial r^2} \right] \quad (10)$$

This equation is solved considering that $C_{A0} = C_{A2}$.

$t > 0$; $r = R_p$, where: $\frac{\partial C_A}{\partial r} = \frac{k_{m2}}{D_{pol} K_p} (C_A^* - C_{ARp})$; Where k_{m2} is the mass transfer coefficient for the external medium, D_{pol} is the diffusivity in the polymer, K_p is the partition coefficient, obtained by a linear relationship between the equilibrium concentration in the solid phase and the concentration in the fluid phase, C_A^* is the equilibrium concentration and C_{ARp} is the concentration of A compound on the surface of the particle.

2.3.2. Mass Balance in Liquid Phase

The mass balance as a function of active ingredient concentration in the solid and liquid phase ("bulk") can be expressed by:

$$V_S \frac{dC_A}{dt} = -V \frac{dC_{Al}}{dt} \quad (11)$$

Where V_S is the volume of the solid phase in the reactor and V is the volume of the liquid phase in the reactor. The equation 11 can be solved in an analytical way, assuming that initially the liquid phase is free of the active principle:

$$C_{Al} = \frac{V_S}{V} (C_{Ai} - C_A) \quad (12)$$

Modeling a Solid matrix that dissolves with time, not changing its Volume

The following model will be presented by a solid matrix that dissolves over time, without changing its volume [14]. A schematic of the problem is shown in Figure 3.

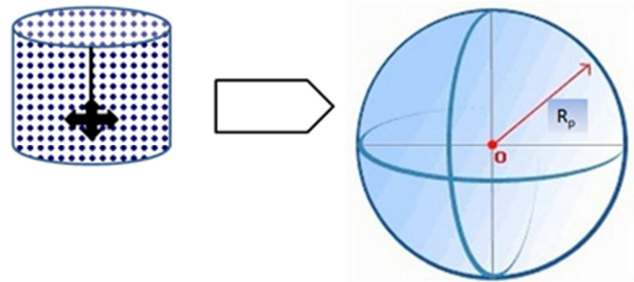


Figure 3. Scheme modeling of the microsphere.

It was assumed in this model that:

- (1) Dissolution was considered as the mechanism that controls the release;
- (2) There was a homogeneous distribution of the active principle in the matrix, during the whole process;
- (3) The concentration varies with time, in medium 1 and medium 2 (Transient);
- (4) The driving force for dissolution shall be defined as the difference between the concentration of the solid active principle and the concentration at the corresponding equilibrium in the liquid phase.

The "Linear Drive Force" equation for this situation is written as:

$$-\frac{dC_A}{dt} = k_d(C_A - K_p C_{Al}) \quad (13)$$

2.3.3. Mass Balance in the Liquid Phase

The mass balance as a function of concentration of active ingredient in the solid phase and the liquid phase ("bulk") can be expressed by:

$$C_{Al} = \frac{V_S}{V} (C_{Ai} - C_A) \quad (14)$$

It is assumed that initially the concentration of active principle in the liquid phase is zero.

Semiempirical Models for the Liberation of Active Principles Used in the Study

- (1) The models that best fit on the experimental data were: Korsmeyers e Peppas
- (2) Weibull

The Korsmeyer-Peppas Model is generally used to analyze the release of active compounds from polymeric microcapsules where the release mechanism is not well known or where more than one type of release mechanism may be involved. Generally 60% of the releases studied fit this model well [2, 15, 16].

This model is used to describe the release of solute when the prevailing mechanism is a combination of the active principle diffusion (Fickian transport) and Case II transport (non-Fickian, controlled by the relaxation of the polymer chains) [17, 18].

In this model, the relationship between release rate and time is equal to:

$$\frac{M_t}{M_\infty} = at^n \quad (15)$$

Where the parameter α is a constant that incorporates structural and geometric characteristics of the microcapsule, n is the release exponent, indicative of the mechanism of release of the active principle, and $\frac{M_t}{M_\infty}$ is the fractional release of the active principle.

The Weibull equation can successfully be applied to almost types of active principle dissolution curves [19]. This model is most useful for the comparison of release of active principles in a system of matrix type [20].

When applied to the dissolution of active principles from microcapsules, the Weibull equation expresses the accumulated fraction of active principle, M_t / M_∞ , in the

solution at the end of time t [21, 22]:

$$\frac{M_t}{M_\infty} = 1 - e^{\left[\frac{-(t-T_i)}{a}\right]^b} \quad (16)$$

In this equation, the α parameter is a parameter related to the time elapsed scale test. The location parameter, T_i , represents the latency time until the dissolution process occurs and, in most cases, is equal to zero, b is the shape parameter that characterizes the curve as being exponential ($b = 1$, Case 1), sigmoid (S-shape) ($b > 1$, Case 2) or parabolic ($b < 1$, Case 3).

The numerical method chosen to solve the model partial differential equations is the finite difference and for linearization of the data to obtain the constant of semiempirical models was used MATLAB, with CFTOOL tool.

Analytical Model for the Liberation of Active Principles Used in this Work.

If the active principle is molecularly dispersed in the matrix, or rapidly or completely dissolved after the solvent has entered the system, the device is called a "monolithic solution" [23–25].

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{\exp\left(-\frac{Dn^2\pi^2t}{Re^2}\right)}{n^2} \quad (17)$$

Where M_t is the concentration of the active principle accumulated in time, M_∞ is the concentration of the active principle accumulated in a time tending to infinity, Re is the external radius of the sphere, D is the diffusion coefficient of the active principle through the system and t is the time.

This analytical equation is derived from the solution of the 2^a. Law of Fick of diffusion, and the following assumptions are made for obtaining [26]:

- (1) Microcapsules do not significantly swell or corrode during the release of the active principle (i.e. no significant change in the matrix carrying the active principle);
- (2) The microcapsules are spherical in shape;
- (3) The active principle is homogeneously distributed inside the microcapsules (beads);
- (4) The release experiment is performed under conditions of perfect immersion;
- (5) The mass transfer resistance due to the boundary layer is negligible compared to the same of diffusion within the microcapsule (sphere) (i.e. the release of the active principle is mainly controlled by diffusion of this through the Microcapsule);
- (6) Dissolution of the active principle is a rapid and complete upon exposure to the solvent;
- (7) The diffusion coefficient is constant regardless of time and position in the microcapsule;
- (8) The release of the active principle is mainly controlled by diffusion of this through the microcapsule.

3. Results

The experimental data used in this study are presented in

the [8] and [27]; are studies of the release of beta-carotene with four different microcapsule compositions using the

Ethyl Acetyl solvent. The different types of microcapsule composition are shown in Table 1.

Table 1. Types of microcapsules in Betacaroteno experiment.

Microcapsule Composition	Nomenclature
Betacarotene: 12 mg.ml ⁻¹ e PHBV: 30 mg.ml ⁻¹	A
Betacarotene: 14 mg.ml ⁻¹ e PHBV: 30 mg.ml ⁻¹	B
Betacarotene: 16 mg.ml ⁻¹ e PHBV: 30 mg.ml ⁻¹	C
Betacarotene: 30mg/ml e PHBV: 30mg/ml	D

The simulated data for ethyl acetate and beta-carotene were obtained using the simulation parameters presented in Table 2.

Table 2. Physicochemical parameters for beta-carotene and ethyl acetate.

Parameter	Molar mass (mg.mol ⁻¹)	Solubility (cal ^{1/2} .cm ^{-3/2})	Molar volume (cm ³ .mol ⁻¹)	Viscosity (g.cm ⁻¹ .s ⁻¹)	Especific mass (g.cm ⁻³)
Betacarotene	536870	8.71	799.2	X	X
Ethyl Acetate	88100	9.10	98.50	0.004	0.897

Fonte: [28–31].

Table 3 shows the physicochemical parameters for beta-carotene and ethyl acetate. The numerical results are presented in Figures 4 to 7, for experiments A, B, C and D, respectively.

Table 3. Physico-chemical parameters for beta-carotene and ethyl acetate.

Parameter	V (ml)	T (K)	D _{AB} (cm ² .s ⁻¹) x10 ⁶	Kp	C ₀ (mg.ml ⁻¹)	Ceq (mg.ml ⁻¹)	V.V _s ⁻¹
Exp. A	30.0	313.15	9.600	367.49	1.33	0.746	289.85
Exp. B	20.0	313.15	9.605	290.84	2.69	0.826	657.89
Exp. C	30.0	313.15	9.605	364.70	4.50	2.469	303.03
Exp. D	30.0	313.15	9.605	995.27	16.26	12.113	341.29

Table 4. Parameters used in the models studied.

Parameter	D _{pol} (cm ² .s ⁻¹)x10 ¹²	v _∞ (cm.s ⁻¹)	R _P (cm) x10 ⁵	Re	Scx10 ⁻³	D _{pol} Analytical (cm ² .s ⁻¹)
Exp. A	2.00	41.86	5.5	0.970	0.494	7.40 x10 ⁻¹⁴
Exp. B	4.10	41.86	5.5	0.413	1.16	3.0x 10 ⁻¹²
Exp. C	4.30	41.86	5.5	0.413	1.16	7.33 x10 ⁻¹³
Exp. D	3.20	41.86	5.5	0.413	1.16	1.18 x10 ⁻¹²

The numerical data statistical analyzes were performed for to identify the correlation between the experimental data and the fitted. The results obtained by the analysis of the F test are shown in Table 5, for A experiment.

Table 5. F test for the models studied in case A (Betacarotene: 12 mg.ml⁻¹ and PHBV: 30 mg.ml⁻¹ and ethyl acetate solvent).

Model Studied	Test F Result	R ²
CDMASSA	1.11	0.96
LDF	1.13	0.97
Weibull	1.00	0.98
Korsmeyer-Peppas	1.21	0.83
Analytical	1.30	0.92

The Figure 4 presents the results obtained by use of the models studied in this work.

By performing an analysis from the F and R2 tests, it can be concluded that the best fitting model was the Weibull model, this model is generally applied when the controlled release is due of matrix type microcapsules [32]. In the

analysis of X2 the models that have good fit were CDMASSA, LDF and Weibull and the best performance are the LDF and CDMASSA where then fit better to the experimental data, comparatively to the model of Weibull, since the last has the limitation of simulating the controlled release but has no kinetic bases [20]. The model that least represented the controlled release was the Korsmeyer-Peppas, possibly because of the type of diffusion it is representing, which is quasi-Fickian, which can be confirmed by parameter n, lower than 0.43, Table 9, where quasi-Fickian release is characterized by the dispersed flow of concentration along the sphere,[33, 34].

The release of the active principle occurred until reaching equilibrium, which was approximately 45%. Note that the Korsmeyer-Peppas model did not present a good mass transfer adjustment since it did not reach equilibrium adequately. The other models provide suitable results with good controlled release behavior of two-phase, quick release and sustained release.

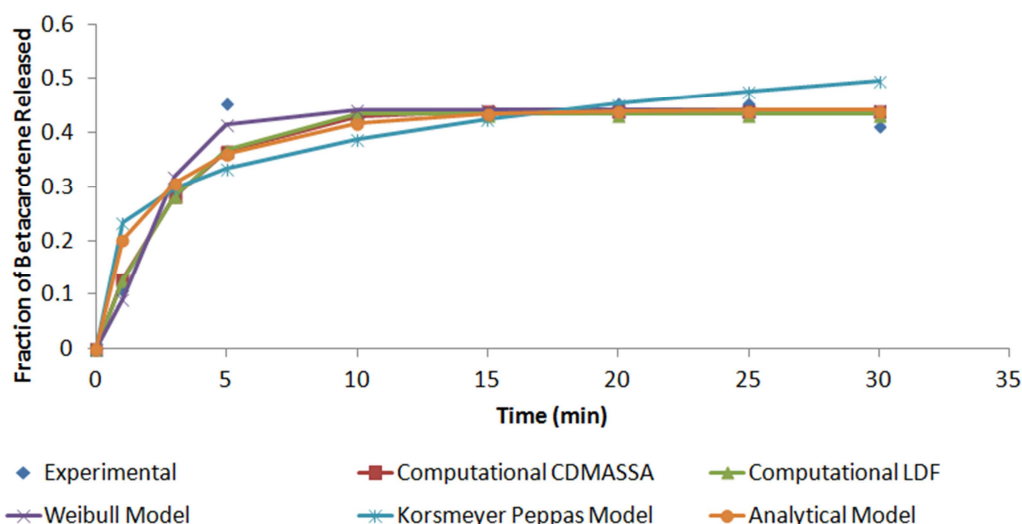


Figure 4. Simulations using the models for experiment A (Beta-carotene: 12 mg.ml^{-1} and PHBV: 30 mg.ml^{-1} and ethyl acetate solvent).

Statistical analyzes were performed to compare the numerical data obtained in this work and the experimental data. Table 6 shows the results obtained from the F and R2 tests for experiment B.

Table 6. F test for the models studied in case B (Betacarotene: 14 mg.ml^{-1} and PHBV: 30 mg.ml^{-1} and ethyl acetate solvent).

Model Studied	Test F Result	R ²
CDMASSA	1.02	0.99
LDF	0.98	0.98
Weibull	1.01	1.00
Korsmeyer-Peppas	1.13	0.89
Solução Monolítica	1.12	0.97

In Figure 5, the results obtained by the use of the models studied in this work are presented.

By performing an analysis from the F and R2 tests it is

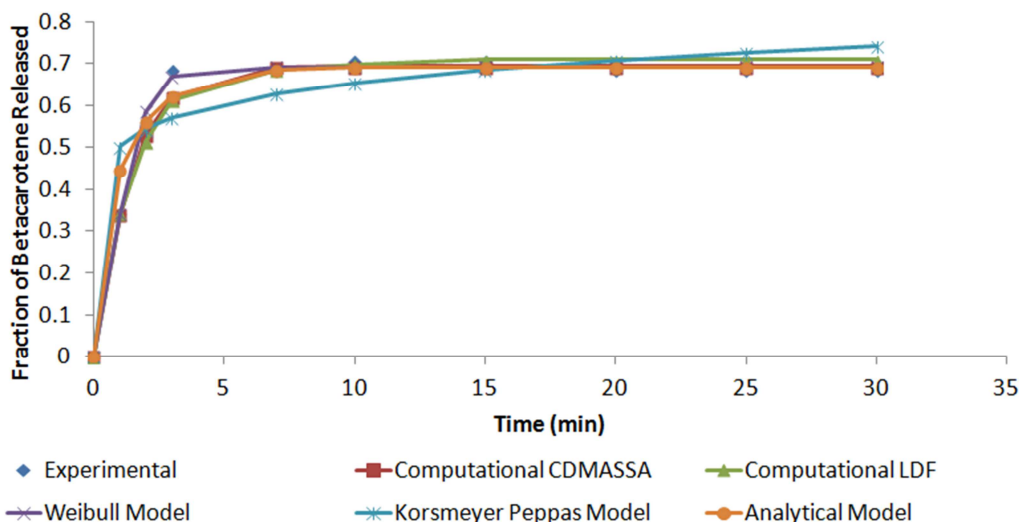


Figure 5. Simulations using the models for experiment B (Betacarotene: 14 mg.ml^{-1} and PHBV: 30 mg.ml^{-1} and ethyl acetate solvent).

Obtaining the numerical data statistical analyzes were performed to identify the correlation between the experimental data and the fitted. The results obtained from

possible to conclude that the best fit model was Weibull which indicates matrix type microcapsules [35], usually the model of Weibull fits very well in most cases studied [36]. The Korsmeyer-Peppas model provided results that did not fit the experimental data so well, if believed to be due to no more than one transport phenomenon involved [37] and the release is only the quasi-Fickian, evidenced by parameter n , Table 9 [33]. The release of the active principle of these microcapsules was close to 70%, which was different from experiment B, evidencing different release structures [24]. The phenomenological model of two phases, fast release followed by constant release was adequate to describe the experimental data; the only model not represented constant phase was the Korsmeyer-Peppas, the results did not achieve constant release.

the F-test analysis are shown in Table 7, for the experiment C.

Table 7. F test for the models studied in case C (Betacarotene: 16 mg.ml⁻¹ and PHBV: 30 mg.ml⁻¹ and ethyl acetate solvent).

Model Studied	Test F Result	R ²
CDMASSA	0.93	0.96
LDF	0.89	0.97
Weibull	1.03	0.98
Korsmeyer-Peppas	1.08	0.95
Solução Monolítica	1.09	0.98

Figure 6 shows the results obtained by using the models studied in this work.

Making an analysis from the F test, it can be concluded that the Weibull model was the best fit and the model actually able to represent the release of better polymer matrix in most cases [36]. Making analysis of the performance of models from R² it can be concluded that in addition to the Weibull model the monolithic solution model also presented a good prediction, which may indicate a delivery model where there

is no erosion [38]. In X2 the Monolithic Solution model adjusted better than the other models, indicating the possibility of no erosion and an initial constant concentration in the microcapsule [39], which possibly does not occur during the release, as the release mechanism must be quasi-Fickian second parameter of the Korsmeyer-Peppas model Table 9 [40]. There was not a worse model that adjusted, as there were good adjustments for some and bad for others. The active principle release of the microcapsule until reaching equilibrium was on the order of 45%, much like experiment C, possibly have the same structure in the microcapsules [41]. Phenomenologically observed that the Korsmeyer-Peppas model gave results that did not reach the equilibrium concentration which is at odds with a two-stage behavior as would be expected (rapid release followed by constant release).

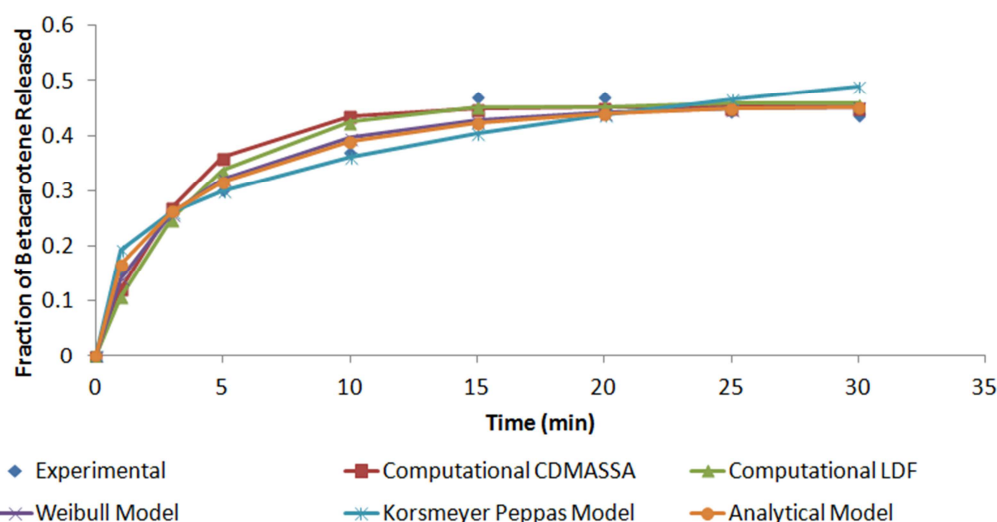


Figure 6. Simulations using the models for experiment C (Betacarotene: 16 mg.ml⁻¹ and PHBV: 30 mg.ml⁻¹ and ethyl acetate solvent).

Obtaining the numerical data statistical analyzes were performed to identify the correlation between the experimental data and the fitted. The results obtained by the analysis of the F test are shown in Table 8, for the D experiment.

Table 8. F test for the models studied in the D case (Beta carotene: 30 mg.ml⁻¹ and PHBV: 30 mg.ml⁻¹ and ethyl acetate solvent).

Model Studied	Test F Result	R ²
CDMASSA	0.96	0.99
LDF	0.96	0.99
Weibull	0.99	0.99
Korsmeyer-Peppas	1.09	0.92
Solução Monolítica	1.06	0.98

Figure 7 shows the results obtained by using the models studied in this work.

Making an analysis from the F test, it can be concluded that the model that best fit was the Weibull, indicating a dissolution of a microcapsule, for this type of situation the

model is well [42]. By performing the best model analysis by the R² values, it can be concluded that the models CDMASSA, LDF and Weibull had a good fit, which may characterize a linear behavior of the diffusion [25].

The studied models presented results for X2 with a good fit to the experimental data. The worst model was of Korsmeyer-Peppas and he characterized through the parameter n, a quasi-Fickian diffusion Table 9 [33], because of this may have presented the worst experimental fit. From the experimental data, it is verified that the release of the active principle reached a close balance of 25%, different behavior of the other microcapsules. Analyzing phenomenologically, it can be observed that the Korsmeyer-Peppas model provided results that do not reach the release equilibrium, which is not what is expected for this two-phase system where there is a rapid and constant after release. The results obtained by the Korsmeyer-Peppas model seem to represent a three-phase system in which there is a fast, slow and constant after release.

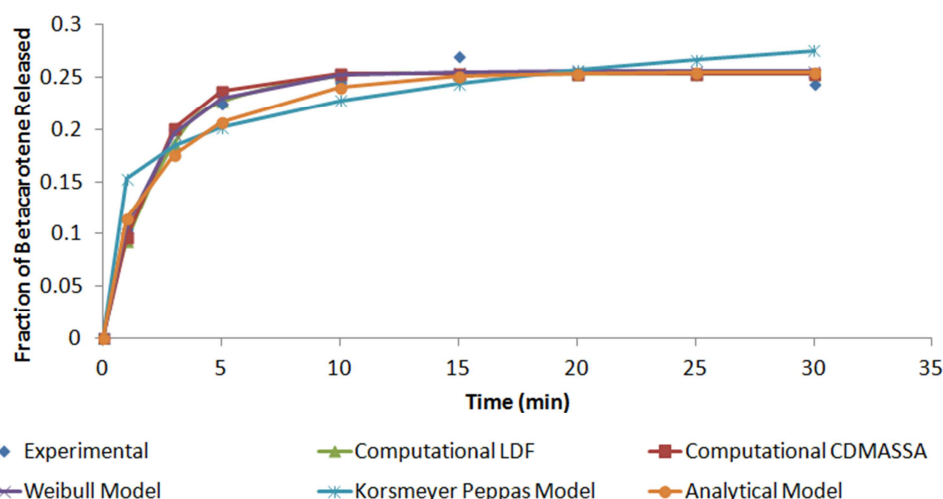


Figure 7. Simulations using the models for the D experiment (Betacarotene: 30 mg.ml⁻¹ and PHBV: 30 mg.ml⁻¹ and ethyl acetate solvent).

The parameters mass transfer coefficient k_{m2} and the diffusivity of the chemical species in the polymer, for each experiment, were obtained through the numerical solution of the models CDMASSA and analytical models and are

presented in Table 9. The dissolution rate k_d was obtained through the LDF model and adjustment parameters were obtained from semiempirical models.

Table 9. Data obtained with the models for experiments A, B, C and D.

Experiments								
A	CDMASSA	LDF		Weibull		Korsmeyer-Peppas		Analytical
	k_{m2} D_{pol}	k_d	a b	a n	D_{pol}			
	0.57 cm.s ⁻¹ 2.00 x 10 ⁻¹² cm ² .s ⁻¹	2.50 x 10 ⁻³ s ⁻¹	2660 s ^b 1.57	0.215 s ⁻ⁿ 0.221	7.40 x 10 ⁻¹⁴ cm ² .s ⁻¹			
B	CDMASSA	LDF		Weibull		Korsmeyer-Peppas		Analytical
	k_{m2} D_{pol}	k_d	a b	a n	D_{pol}			
	0.57 cm.s ⁻¹ 4.10 x 10 ⁻¹² cm ² .s ⁻¹	0.008 s ⁻¹	563.70 s ^b 1.453	0.459 s ⁻ⁿ 0.114	3.00 x 10 ⁻¹² cm ² .s ⁻¹			
C	CDMASSA	LDF		Weibull		Korsmeyer-Peppas		Analytical
	k_{m2} D_{pol}	k_d	a b	a n	D_{pol}			
	0.57 cm.s ⁻¹ 1.80 x 10 ⁻¹² cm ² .s ⁻¹	0.002 s ⁻¹	55.33 s ^b 0.738	0.139 s ⁻ⁿ 0.272	7.33 x 10 ⁻¹³ cm ² .s ⁻¹			
D	CDMASSA	LDF		Weibull		Korsmeyer-Peppas		Analytical
	k_{m2} D_{pol}	k_d	a b	a n	D_{pol}			
	0.52 cm.s ⁻¹ 3.20 x 10 ⁻¹² cm ² .s ⁻¹	0.002 s ⁻¹	73.53 s ^b 0.901	0.293 s ⁻ⁿ 0.1739	118 x 10 ⁻¹² cm ² .s ⁻¹			

The Weibull model presented the best fit for these experimental data, in the 14th different semiempirical models defined, and the Korsmeyer-Peppas model was used, because its fit can represent the phenomenology of the controlled release.

For experiment A, B, C and D, by analyzing the Korsmeyer-Peppas model, the n constant was less than 0.43, indicating a quasi-Fickian transport mechanism within the microcapsule.

The minimum active principle release for the solvent microcapsule system (ethyl acetate) in the experiments studied was 25% and at most 75%, which shows that the solvent microcapsule system interferes with the controlled release of active principles, since there was variation of the release fraction in the experiments and this difference can be attributed to the formation nature of the microcapsule [43]. The diffusivity of the medium polymer adjusted with the CDMASSA model was around 2.7 x 10⁻¹² cm².s⁻¹ for the PHBV polymer in a solution of ethyl acetate with the diffusion of beta-carotene and with the model of Monolithic Solution the diffusivity value was 1.54 x 10⁻¹² cm².s⁻¹. The

average dissolution rate adjusted with the LDF model was around 3.6 x 10⁻³ s⁻¹ for PHBV in ethyl acetate solution with the dissolution of beta-carotene.

4. Conclusion

Observing the data obtained in the simulation, it can be concluded that the models studied presented a significant condition of representation of the experiments analyzed, showing that the choice of models where there is diffusion of Fickian origin, LDF and semiempirical models was adequate for the description of the experimental data.

Most of the time, the best adjustments to the experimental data were those obtained by the semi-empirical models, but this was already expected because they are usually curve-fit equations for specific conditions of the experiment and not a set of phenomenologically constructed equations, such as case of the CDMASSA models and the LDF simpler. The models used fit well with the results of the experiments from the PHBV tests found in the literature. The different polymer structures and their respective forms of production determine

the morphological characteristics of the system-particle-solvent that greatly interfere in the results of the experiments,

especially in the equilibrium fractions of release and time to reach these releases.

Symbology

a [$-t^{-n}$] Equação 15	Constant that incorporates structural and geometric characteristics of the pharmaceutical form
A [-] Equação 15	Parameter of the contribution of the burst effect
B [-] Equação 15	Contribution parameter of the continuous release phase
C [$M.L^{-3}$]	Concentration of solute
C_A [$mol.L^{-3}$]	Molar concentration of species A
C_A^* [$mol.L^{-3}$]	Molar concentration of species A in equilibrium
C_{Ai} [$mol.L^{-3}$]	Molar concentration of species A in the liquid phase
C_{Ai} [$mol.L^{-3}$]	Initial Molar concentration of the initial A
C_{A2} [$mol.L^{-3}$]	Molar concentration of species A in the fluid phase
C_{ARp} [$mol.L^{-3}$]	Molar concentration of species A in radius R_p
C_{eq} [$M.L^{-3}$]	Mass balance concentration
C_l [$M.L^{-3}$] Figura 1	Concentration of liquid phase
C_{ms} [$M.L^{-3}$]	Solubility of the active substance in the matrix
\hat{C}_p [energia. T^{-1}]	Heat capacity
C_s [$M.L^{-3}$] Figura 1	Solid phase mass concentration
C_0 [$M.L^{-3}$]	Initial mass concentration of active principle in the particle
D_{AB} [$L^2.t^{-1}$]	Mass diffusivity of solute A in medium B
D_{ABWC} [$L^2.t^{-1}$]	Diffusivity of solute A in middle B of the Wilke-Chang model
D_{AP} [$L^2.t^{-1}$]	Diffusivity of solute A in the polymer
D_m [$L^2.t^{-1}$]	Mass diffusivity
D_{pol} [$L^2.t^{-1}$]	Diffusivity of the active principle in the polymer
Diam[L]	Diameter of sphere
F [-]	F-number of the statistical test F
k_B [$L^2.M.t^{-2}.T^{-1}$]	Boltzmann constant
k_{m2} [$L.t^{-1}$]	Mass transfer coefficient
K [$M.t^{-1}$]	Proportionality constant
kd [t^{-1}]	Coefficient representing mass transfer rate
K_p [-]	Partition coefficient
M_B [$M.mol^{-1}$]	Molar mass of B
M_∞ [$M.mol^{-1}$]	Saturated molar mass in solution
n [-]	Release exponent
q [$M.L^{-3}$]	Mass concentration in the solid phase
r [L]	Particle radius
r_0 [L]	Radius of spherical matrix
r_A [L]	Radius of molecule A
R [Energia. $mol^{-1}.T^{-1}$]	Universal gas constant
R_p [L]	Particle radius
Re [-]	Reynolds number
Sch [-]	Schmidt's number
t [t]	Time
T [T]	Temperature
v_∞ [$L.t^{-1}$]	Average speed
V [L^3]	Volume of liquid
V_{bA} [$L^3.mol^{-1}$]	Molecular volume of A
V_i [$L^3.mol^{-1}$]	Molecular volume of A or B
V_s [L^3]	Volume of solid
x_A [-]	Molar fraction of A
Greek letters	
α [$-t^{-1}$]	Kinetic rate constant
β [$-t^{-1}$]	Kinetic rate constant
δ_i [$M.L^{-3}$]	Solubility of A or B
ε [-]	Matrix Porosity

μ_B [M.L ⁻¹ .t ⁻¹]	Dynamic Viscosity
ρ [M./L ⁻¹]	Density
τ [-]	Tortuosity factor of capillary system
γ_A [-]	Coefficient of Activity of A

Abbreviations

Energy	Energy unit
L	Size unit of space
LDF	Linear Drive Force
M	Mass unit
PHBV	Poli (3-hidroxitbutirato-co-3-hidroxitvalerato)
t	Time unit
T	Temperature unit
-	Dimensionless

References

- [1] L. Calabuig-Jiménez, E. Betoret, N. Betoret, F. Patrignani, C. Barrera, L. Seguí, R. Lanciotti, M. Dalla Rosa, High pressures homogenization (HPH) to microencapsulate *L. salivarius* spp. *salivarius* in mandarin juice. Probiotic survival and in vitro digestion, *J. Food Eng.* 240 (2019) 43–48. doi:10.1016/j.jfoodeng.2018.07.012.
- [2] D. França, Â. F. Medina, L. L. Messa, C. F. Souza, R. Faez, Chitosan spray-dried microcapsule and microsphere as fertilizer host for swellable – controlled release materials, *Carbohydr. Polym.* 196 (2018) 47–55. doi:10.1016/j.carbpol.2018.05.014.
- [3] E. Cussler, Diffusion: mass transfer in fluid systems, 3rd ed., Cambridge University Press, 2009. <http://medcontent.metapress.com/index/A65RM03P4874243N.pdf> (accessed October 10, 2015).
- [4] S. N. Rodrigues, I. M. Martins, I. P. Fernandes, P. B. Gomes, V. G. Mata, M. F. Barreiro, a. E. Rodrigues, Scentfashion®: Microencapsulated perfumes for textile application, *Chem. Eng. J.* 149 (2009) 463–472. doi:10.1016/j.cej.2009.02.021.
- [5] N. Agnihotri, R. Mishra, C. Goda, M. Arora, Microencapsulation – A Novel Approach in Drug Delivery : A Review, 2 (2012) 1–20.
- [6] M. Ahmad, P. Mudgil, A. Gani, F. Hamed, F. A. Masoodi, S. Maqsood, Nano encapsulation of catechin in starch nanoparticles: Characterization; release behavior and bioactivity retention during in-vitro digestion, *Food Chem.* (2018). doi:10.1016/j.foodchem.2018.07.024.
- [7] Q. Lin, R. Liang, P. A. Williams, F. Zhong, Factors affecting the bioaccessibility of β -carotene in lipid-based microcapsules: Digestive conditions, the composition, structure and physical state of microcapsules, *Food Hydrocoll.* 77 (2018) 187–203. doi:10.1016/j.foodhyd.2017.09.034.
- [8] W. L. Priamo, A. M. de Cezaro, S. C. Benetti, J. V. Oliveira, S. R. S. Ferreira, In vitro release profiles of β -carotene encapsulated in PHBV by means of supercritical carbon dioxide micronization technique, *J. Supercrit. Fluids.* 56 (2011) 137–143. doi:10.1016/j.supflu.2010.12.013.
- [9] S. V Patankar, Numerical Heat Transfer and Fluid Flow, Hemisphere Publishing Corporation, 1980. <http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Numerical+heat+transfer+and+fluid+flow#0>.
- [10] G. Frenning, A. Alderborn, Modelling of drug release from coated granular pellets, *J. Control. Release.* 92 (2003) 113–123.
- [11] S. Basu, D. Banerjee, R. Chowdhury, P. Bhattacharya, Controlled release of microencapsulated probiotics in food matrix, *J. Food Eng.* (2018). doi:S0260877418302553.
- [12] C. R. Wilke, P. Chang, Correlation of diffusion coefficients in dilute solutions, *AIChE J.* 1 (1955) 264–270. doi:10.1002/aic.690010222.
- [13] R. B. Bird, W. E. Stewart, E. N. Lightfoot, Transport Phenomena, John Wiley & Sons, 2007. doi:10.1051/jp4:20020462.
- [14] M. Polakovič, T. Görner, R. Gref, E. Dellacherie, Lidocaine loaded biodegradable nanospheres: II. Modelling of drug release, *J. Control. Release.* 60 (1999) 169–177. <http://www.sciencedirect.com/science/article/pii/S0168365999000127> (accessed October 26, 2014).
- [15] N. Peppas, J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, *Int. J. Pharm.* 57 (1989) 169–172. <http://www.sciencedirect.com/science/article/pii/0378517389903062> (accessed January 16, 2015).
- [16] N. L. Vanden Braber, A. J. Paredes, Y. E. Rossi, C. Porporatto, D. A. Allemandi, C. D. Borsarelli, S. G. Correa, M. A. Montenegro, Controlled release and antioxidant activity of chitosan or its glucosamine water-soluble derivative microcapsules loaded with quercetin, *Int. J. Biol. Macromol.* 112 (2018) 399–404. doi:10.1016/j.jbiomac.2018.01.085.
- [17] P. L. Ritger, N. A. Peppas, A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, *J. Control. Release.* 5 (1987) 23–36.
- [18] P. L. Ritger, N. A. Peppas, A simple equation for description of solute release II. Fickian and anomalous release from swellable devices, *J. Control. Release.* 5 (1987) 37–42.

- [19] P. Costa, J. S. Lobo, Modeling and comparison of dissolution profiles, *Eur. J. Pharm. Sci.* (2001). <http://www.sciencedirect.com/science/article/pii/S0928098701000951> (accessed January 19, 2015).
- [20] F. Langenbucher, Handling of computational in vitro / in vivo correlation problems by Microsoft Excel II. Distribution functions and moments, *Eur. J. Pharm. Biopharm.* 55 (2003) 77–84. doi:10.1016/S0.
- [21] D. Y. Arifin, L. Y. Lee, C.-H. Wang, Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems., *Adv. Drug Deliv. Rev.* 58 (2006) 1274–325. doi:10.1016/j.addr.2006.09.007.
- [22] S. Dash, P. N. Murthy, L. Nath, P. Chowdhury, Kinetic Modeling on Drug Release From Controlled Drug Delivery Systems, *Acta Pol. Pharm. - Drug Res.* 67 (2010) 217–223.
- [23] J. Siepmann, F. Siepmann, Mathematical modeling of drug delivery., *Int. J. Pharm.* 364 (2008) 328–43. doi:10.1016/j.ijpharm.2008.09.004.
- [24] J. Siepmann, F. Siepmann, Modeling of diffusion controlled drug delivery., *J. Control. Release.* 161 (2012) 351–62. doi:10.1016/j.jconrel.2011.10.006.
- [25] E. Nuxoll, Added release time in diffusion/dissolution coupled release., *Int. J. Pharm.* 494 (2015) 195–204. doi:10.1016/j.ijpharm.2015.08.017.
- [26] J. Crank, The mathematics of diffusion, 2nd ed., Oxford University Press, 1975. <http://books.google.com/books?hl=en&lr=&id=eHANhZwVo uYC&oi=fnd&pg=PA1&dq=The+Mathematic+of+Diffusion&ots=fy-4y-jlOW&sig=7bUh2HpsFuO4NpDhsyIGWDlulF0> (accessed October 10, 2015).
- [27] W. L. Priamo, A. M. de Cezaro, S. R. S. Ferreira, J. V. Oliveira, Precipitation and encapsulation of β -carotene in PHBV using carbon dioxide as anti-solvent, *J. Supercrit. Fluids.* 54 (2010) 103–109. doi:10.1016/j.supflu.2010.02.013.
- [28] A. F. M. Barton, Solubility parameters, *Chem. Rev.* 75 (1975) 731–753. doi:10.1021/cr60298a003.
- [29] L. Feltl, V. Pacakova, K. Stulik, K. Volka, Reliability of Carotenoid Analyses: A Review, *Curr. Anal. Chem.* 1 (2005) 93–102. doi:10.2174/1573411052948424.
- [30] A. Paar, Viscopedia, Viscopedia. (2015).
- [31] Royal Society of Chemistry, ChemSpider, R. Soc. Chem. (2015).
- [32] A. D. S. M. R. Pascoal, P. M. da Silva, M. N. Coelho Pinheiro, Drug dissolution profiles from polymeric matrices: Data versus numerical solution of the diffusion problem and kinetic models, *Int. Commun. Heat Mass Transf.* 61 (2015) 118–127. doi:10.1016/j.icheatmasstransfer.2014.12.011.
- [33] S. Sahoo, C. K. Chakraborti, P. K. Behera, Development and Evaluation of Gastroretentive Controlled Release Polymeric Suspensions Containing Ciprofloxacin and Carbopol Polymers, *J. Chem. Pharm. Res.* 4 (2012) 2268–2284.
- [34] F. W. Deng, J. H. Cushman, Comparison of moments for classical-, quasi-, and convolution- Fickian dispersion of a conservative tracer, *Water Resour. Res.* 31 (1995) 1147–1149.
- [35] P. Costa, J. M. Sousa Lobo, Evaluation of mathematical models describing drug release from estradiol transdermal systems., *Drug Dev. Ind. Pharm.* 29 (2003) 89–97. doi:10.1081/DDC-120016687.
- [36] J. R. Medina, D. K. Salazar, M. Hurtado, A. R. Cortés, A. M. Domínguez-Ramírez, Comparative in vitro dissolution study of carbamazepine immediate-release products using the USP paddles method and the flow-through cell system., *Saudi Pharm. J.* 22 (2014) 141–7. doi:10.1016/j.jsps.2013.02.001.
- [37] P. Costa, J. M. Sousa Lobo, Modeling and comparison of dissolution profiles, *Eur. J. Pharm. Sci.* 13 (2001) 123–133. doi:10.1016/S0928-0987(01)00095-1.
- [38] H. Umer, H. Nigam, A. M. Tamboli, M. S. M. Nainar, Microencapsulation : Process, Techniques and Applications, *Int. J. Res. Pharm. Biomed. Sci.* 2 (2011) 474–481.
- [39] I. a. Kouskoumvekaki, J. Abildskov, Thermodynamic Modelling as a Tool in the Design of Microsphere Controlled-Delivery Systems, *Chem. Eng. Res. Des.* 84 (2006) 652–663. doi:10.1205/cherd06023.
- [40] E. S. El-leithy, D. S. Shaker, M. K. Ghorab, R. S. Abdel-rashid, Optimization and characterization of diclofenac sodium microspheres prepared by a modified coacervation method, *Drug Discov. Ther.* 4 (2010) 208–216.
- [41] L. N. Carli, T. S. Daitx, O. Bianchi, J. S. Crespo, R. S. Mauler, Influence of the thermal degradation on the formation of the lamellar structure of PHBV evaluated by time-temperature resolved SAXS experiments, in: XIVSLAP/XII CIP, 2014: pp. 10–13.
- [42] A. Dokoumetzidis, P. Macheras, A century of dissolution research: from Noyes and Whitney to the biopharmaceutics classification system., *Int. J. Pharm.* 321 (2006) 1–11. doi:10.1016/j.ijpharm.2006.07.011.
- [43] P. S. C. Sacchetin, R. F. Setti, P. D. T. V. E. Rosa, Â. M. Moraes, Properties of PLA/PCL particles as vehicles for oral delivery of the androgen hormone 17 α -methyltestosterone, *Mater. Sci. Eng. C.* 58 (2016) 870–881. doi:10.1016/j.msec.2015.09.071.