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Determination of diffusion coefficients of glycerol and glucose from starch based thermoplastic compounds on simulated physiological solution

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Blends of corn starch with poly(ethylene-vinylalcohol) copolymer (SEVA-C) have been studied and reported as biodegradable. These materials are known to be sensitive to enzymatic action, evidencing a degradation of the starch phase in α-amylase assays. However, from the physical-chemical point of view the degradation of the blend is mainly associated with the leaching of glycerol, since other compounds are not released and no carbohydrates were found in the degradation solution. Based on these results, the present work attempts to determinate the respective diffusion coefficients. Four different experiments were performed, using samples with different thicknesses that were immersed in a simulated physiological solution. High performance liquid chromatography (HPLC) was used to separate the sugar derivatives and glycerol from the degradation solutions. The obtained data were fitted to an empirical model to allow the estimation of the diffusion coefficient for glycerol and glucose, based on the analytical solution for Fick's law of diffusion, and a good agreement was found ($R^2 \approx 1$). The glycerol leaches quickly out during the first few days of immersion, stabilizing thereafter, presenting greater diffusion coefficients for thicker samples. As the quantity of saccharides in the solution remains almost invariable along the experiments, this work also confirms that the degradation process is difficult without the action of enzymes.

1. Introduction

Blends of native corn starch with poly(ethylene-vinyl alcohol) copolymer (SEVA-C), are potential alternatives to the biodegradable polymers used in clinical applications [1–6] due to their degradation behaviour [7–11] and properties [4–6], namely their biocompatibility with the organic tissues and their similarity with the bone dynamic mechanical behaviour [1]. SEVA-C is a thermoplastic blend of corn starch with poly(ethylene-vinylalcohol) copolymer. As a biomaterial it is composed of a natural molecule, starch as it is generally biodegradable, inexpensive and unfailing source of raw material. Glycerol is used in the blend as a plasticizer, involving the two phases, starch and the synthetic poly(ethylene-vinylalcohol) [2].

In general, a polymeric system must be specifically engineered to meet stringent demands [12] being the polymer degradability one of the most important factors leading to the acceptability of polymers for medical use [13].

Many synthetic and modified natural biodegradable polymers are in use today for temporary orthopaedic prosthetic uses, e.g.: reconstituted collagen, fibrin, poly(glycolic acids) and poly(lactic acids). The use of biodegradable polymers is advantageous, but specific problems such as toxicity of the degradation products and the influence of the degradation of the matrix on the release rate have to be investigated before application [14]. The material must be developed with a degradation rate adequate to retain the scaffold strength until

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the newly grown tissue takes over the synthetic support [15–18].

Furthermore, the degradation process of a biodegradable polymer and the effects that the correspondent degradation products might have on the body are crucial for long-term success of a biomaterial [19].

The degree of success in bone tissue engineering is highly dependent on the properties of the scaffold. Basic scaffold design requirements include degradability, biocompatibility, high surface area/volume ratio and mechanical integrity. The main goal is to develop a biocompatible scaffold material which is degradable over a controllable time scale into non-toxic degradation products, which may disappear simultaneously with new bone formation, leaving natural tissue replacement [20–22].

In the past decades, numerous methodologies have been investigated in order to produce controlled-release devices presenting zero-order release kinetics over a prolonged period of time [23–28]. The controlled release of components can be achieved using biodegradable polymers as physical carriers. The leaching of components from the polymeric matrix is governed by diffusion and/or degradation of polymers [16].

It has been shown with starch-based scaffolds that porosity has a great influence on the delivering of the model, being possible to control the release profile with this material property [29]. The release was controlled in the first stage by diffusion and in the second stage by the matrix degradation.

First-order release kinetics is generally expected. Nevertheless, more complex kinetics has been frequently observed since diffusion is dependent on the degradation of the matrix [14], and the physicochemical properties of polymers also control the delivery kinetics [30–32].

Diffusion is probably the most important mechanism of solute transport through material thickness and it is generally described using a single parameter, the effective diffusivity (D). For an ideal solution or a dilute solution, the flux (J) reduces to Fick's first law:

$$J = -D\frac{dC}{dx} \tag{1}$$

where C is the bulk solute concentration and x the axial coordinate.

D cannot be obtained directly since the concentrations of the solute inside the material are not measurable. The concentrations inside the material can be related to the concentrations in the adjacent solution, by the following equations for a steady state:

$$J = -D\frac{\Delta C}{l} \tag{2}$$

where l is the thickness material [14].

The diffusion mass transfer process can be represented by the Fick's second law:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{3}$$

The solution of Fick's second law can be used as a method to estimate the diffusion coefficient.

The polymer permeability is dependent on several factors including the material chemical structure of the developed morphology. The transport of permeants is affected by the swelling properties of the material, being assumed that the permeating species are not miscible in the crystalline phase and are transported only throughout the amorphous regions. Tortuosity and porosity are additional physical factors for assessing solute permeation. Two basic mechanisms have commonly been considered in explaining solute transport through a polymer: the "pore" mechanism and the "partition". In the pore mechanism, solute transport occurs via diffusion through microchannels or pores that exist within the polymer network. In the partition mechanism, solute transport is presumed to occur by a process involving dissolution of the solute within the polymer followed by diffusion along and between the polymer chains [14].

The objective of this work is to determine the effective diffusivities of two important components (glycerol and glucose) in SEVA-C samples of different thickness. The diffusion coefficient through the matrix was computed from the partial differential equation of diffusion. The values were assessed measuring the leaching of those compounds to the solution. The mathematical procedures for data analysis were applied to confirm the calculated values as well as the suitability of the experimental design, ignoring the eventual external mass transfer.

2. Materials and methods

2.1. Materials

The material studied was a thermoplastic blend of corn starch with a poly(ethylene-vinyl alcohol) copolymer (60/40 mol/mol), SEVA-C, supplied by Novamont (Novara, Italy). The typical amount of starch in this commercially available blend is 50–60% (wt%). Injection moulded square plates 30 mm wide and 2 mm thick were used for the assays.

Four different randomly selected batches were tested using 1, 10, 15 and 20 SEVA-C samples in different containers, considered as batches 1, 2, 3 and 4, respectively. Fig. 1(a) and (b) shows the setup of the samples in each tube. This system has been designed, especially for the evaluation of kinetic diffusion parameter, and the possible influence of thickness on the release process.

The SEVA-C samples, were immersed 30 days at pH 7.4 and 37 $\pm$ 1 °C in individual containers (volume approximately 50 cm^3), under continuous shaking (150 r.p.m.), with a Hank's balanced salt solution (HBSS) without phenol red (HBSS Sigma reference H8264).

At preset times, 1 ml of each solution was taken out and the corresponding batch neglected, in order to avoid errors owing to the difference of liquid volume, that could interfere with the steady-state establish. In this way, each batch was used for a single sampling.

The specimens for the different batches were sterilized before the assay, by autoclaving in a 10/90 mixture of ethylene oxide (EtO) and carbon dioxide (CO_2), with a cycle time of 20–22 h at a working temperature of 45 °C, and a chamber pressure of 180 kPa.

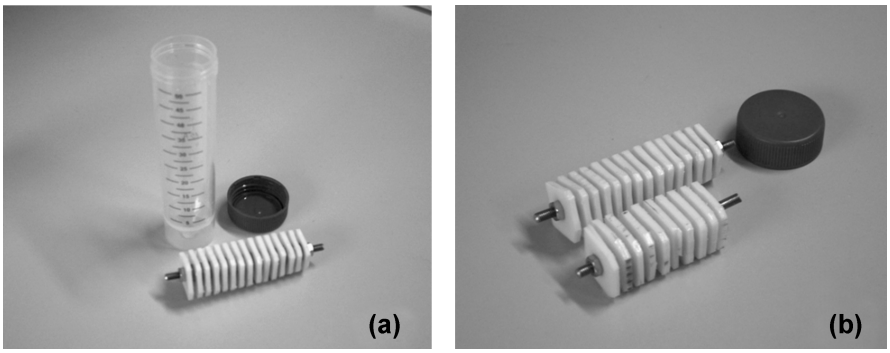

Figure 1 Batches 2 and 3 performed with 15 (a) and 10 (b) specimens, respectively.

2.2. Analytical methods

2.2.1. Detection of starch and polysaccharides

The starch amount in the degradation solutions was determined by means of a simple colorimetric method. 300 μl of sulphuric acid 2 M and 0.5 ml of KI-I_2 were added to a 5 ml of sample of the respective solution. The absorbance of the resulting solution was determined by ELISA (microprocessor controlled readers in 96 well microplates) at a wavelength of 580 nm, being the respective concentration obtained from a standard curve, obtained with the same corn starch used in the samples. A solution of HBSS without SEVA-C specimen was used as control for the blank cells.

The total amount of polysaccharides in the degradation solutions was quantified using the Dubois method [33], which is based on the addition of 1 ml of phenol (5% w/v) and 5 ml sulphuric acid (95–97%) to 1 ml of sample of the degradation solution. The absorbance of the resulting mixture was determined with an ELISA at a wavelength of 490 nm, using the control sample as the reference cell.

2.2.2. Detection of reducing sugars

During the course of the experiments, the saccharides concentration was measured. The reducing sugars in the degradation solutions were quantified by the dinitrosalicylic acid method: 0.5 ml of reagent DNS was added to 0.5 ml of the sample to be analysed [34]. At the same time the blank was prepared using 0.5 ml of control sample. As previously, HBSS without SEVA-C was used as control. The mixture was heated at 100 °C for 10 min. After cooling to room temperature, 5 ml of distilled water were added, and the absorbance at 540 nm was measured in the ELISA reader. The respective carbohydrate concentration was obtained by comparison with a standard curve.

2.2.3. Oligosaccharides and glycerol detection by high performance liquid chromatography

High performance liquid chromatography (HPLC) with 830-RI (Jasco, Japan) refraction index detection and a 880-PU pump was used to separate the sugar derivatives and glycerol from the degradation solutions.

Commercial standards were used for the calibration of the Chrompack carbohydrates Ca column. A Chrompack guard column at 90 °C with ultra-pure water as eluent (0.5 ml/min) was maintained at 6500–7000 kPa. The eluent was filtered through a 0.2 μm sterilized membrane degassed with helium prior to be used, and kept in a container that precludes introduction of airborne bacterial and fungal contamination. Sorbitol (1 g/l) was used as the internal standard. Prior to the injection, the samples were filtered through 0.22 mm filters (Milipore) to remove the particles present in the degradation solutions. Three replica of each sample were performed. A standard curve was previously built using different standard concentrations.

2.3. Data treatment: Analytical approach

If the hydrodynamic conditions around the objects are well characterised, it is possible to apply empirical correlations to calculate D. Correlations are available only for sphere, infinite cylinder and plane sheet geometry, together with the need of very well defined hydrodynamic conditions. The solution of the correlations depends, among other factors, on the geometry of the object under study and on the boundary conditions; several parameters were changed, including: sample thickness as described above, in order to investigate their influence on the concentration profiles.

Fick's modelling is adapted to passive diffusion systems where the diffusion coefficients may be supposed to be constant, without modification of the properties of the polymer during the release.

The diffusion mass transfer process that occurs through the thickness of each suspended specimen, assuming that the bulk solution is well mixed, and the component concentrations are the same at the surface of the material and the bulk solution, is represented by the Fick's diffusion equation:

$$\frac{\partial C'}{\partial t} = D\frac{\partial^2 C'}{\partial x^2} \tag{4}$$

with C' defined as:

$$C'(t) = C_0 - C(t)$$

where $C(t)$ is the bulk solute concentration at the time t, C_0 the initial surface sheet solute concentration, and D the diffusion coefficient. The sheet occupies the space

$-l \leq x \leq l$ (axial coordinate) being $2l$ the material thickness.

For the problem of desorption from the sheet the chosen initial and boundary conditions are:

$$\begin{aligned} t = 0, \quad & -l < x < l \quad C'(t) = C_0 \\ t > 0, \quad & x = \pm l \quad a\frac{\partial C'}{\partial t} = \pm D\frac{\partial C'}{\partial x} \\ t > 0, \quad & x = 0 \quad \frac{\partial C'}{\partial x} = 0 \end{aligned}$$

The second condition implies perfect mixing of the liquid phase around the particle, i.e., no external mass transfer resistance. For this set of conditions, and assuming plane sheet geometry, the analytical solution for Equation 4 using Laplace transform [35] is as follows:

$$\frac{C'_t}{C'_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2.q_n^2} \exp\left(\frac{-Dq_n^2 t}{l^2}\right) \quad (5)$$

C'_t and C'_∞ are the bulk solute concentration at time t and t_∞, respectively.

q_n are the non-zero positive roots of:

$$\tan(q_n) = -\alpha q_n$$

Alpha (α) is defined as the ratio between the volumes of solution (a) and sheet (l), as demonstrated in the scheme of Fig. 2.

The release kinetics to the solution of glucose and glycerol was studied, for the different batches, during 30 days of immersion. Each batch contains different number of specimens that correspond to different alpha and thickness values (Table I). From measurements, the specimen thickness and the data set for desorption, for each immersion time, were determined and used as input data.

The values of the diffusion coefficient (D) for glucose and glycerol were determined based on the analytical solution for Fick's law of diffusion (Equation 5). They are obtained applying a suitable least square procedure using an implicit formulation with the function of the sum of squared residues, between the calculated and measured concentrations (Fig. 3). The function "nonlinfit" from Statistic Toolbox of Matlab 6.5 (The Mathworks, USA) was used for finding parameter estimates in nonlinear modelling. This function finds the parameter (D) that minimizes the sum of the squared differences between the observed responses and there fitted values. It uses the Gauss-Newton algorithm with Levenberg-Marquardt modifications for global convergence. The function "nlparci" was used to obtain 95% confidence intervals on the parameter estimates based on asymptotic normal distribution for the parameter estimate [36]. The coefficient of determination, R^2, was also evaluated to account for the proportion of variation in the dependent variable that has been accounted for by the regression curve.

The model described assumes that:

- The sheet is suspended in a volume of solution so large that the amount of solute taken up by the sheet is a negligible fraction of the whole, and the solution is well stirred, i.e., the concentration in the solution remains constant.

TABLE I Values of alpha (α) and half thickness (l) for each batch

Batches	α	l (m)
1	49.0	0.0015
2	4.0	0.0115
3	2.33	0.01725
4	1.50	0.0230

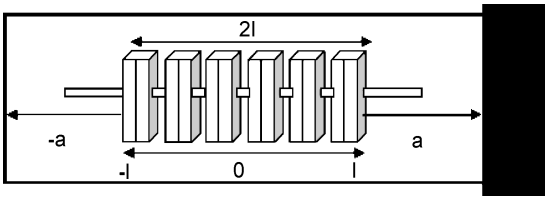

Figure 2 Size dimensions (l, a) for a plane sheet inside a tube.

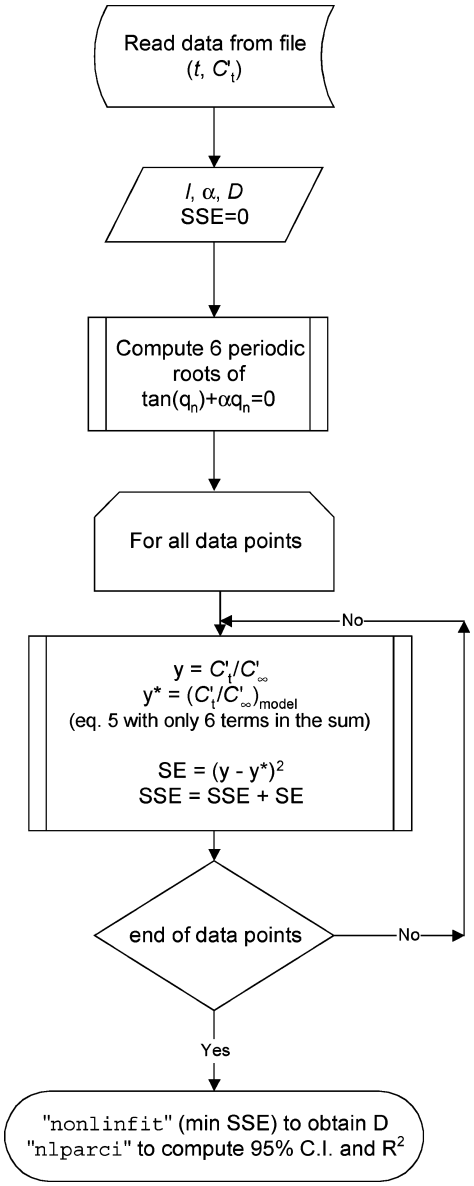

Figure 3 Flowsheet for the computation of diffusion coefficients from Equation (5) using a least square procedure.

- The solution is well stirred, so the concentration in the solution depends only on time, and is essentially determined by the condition that the total amount of solute in the solution and in the sheet remains constant as diffusion proceeds.
- The concentration of solute at the surface of the sheet is the same as that in the solution.

3. Results

Fig. 4 shows the concentration of starch leached to the solution for batch 1, including only one specimen. No more batches were performed, since there was no leaching of starch.

Glucose diffuses along the immersion time through SEVA-C specimens to the solution according to the concentration profiles on Figs. 5–7. The figures show the curves obtained from the three analytical methods used: polysaccharides quantification, DNS and HPLC, enabling to compare and quantify all the saccharides in solution.

At the same time, the glycerol quantification was performed by HPLC and the results obtained are present on Fig. 8 for all the batches tested. The results evidence that glycerol was the only compound leached, as compared with the concentration profiles of other compounds in the degradation solutions.

The solute diffusion coefficients were determined through diffusion studies in HBSS. Glucose and glycerol diffused from both the top and bottom surfaces

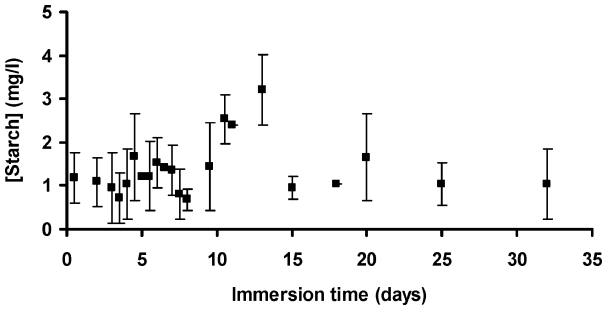

Figure 4 Concentration of starch in 50 ml of solution for batch 1, as a function of immersion time. Each value represents the mean of 2 duplicates (4 values in all); error bars are 95% confidence intervals of each mean.

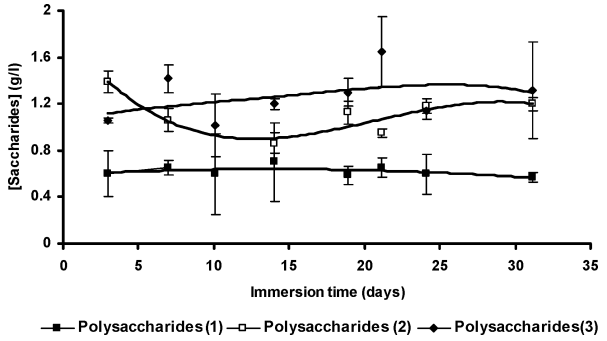

Figure 5 Concentration of polysaccharides in 50 ml of solution, for batch 1(■), 2(□) and 3(♦), as function of immersion time. Each value represents the mean of 2 duplicates (4 values in all); error bars are 95% confidence intervals of each mean.

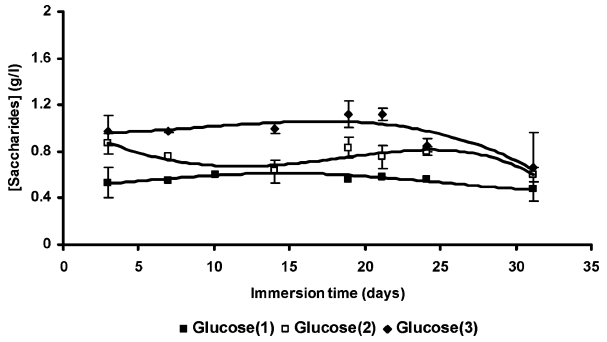

Figure 6 Concentration of glucose from DNS method in 50 ml of solution, for batch 1(■), 2(□) and 3(♦), as function of immersion time. Each value represents the mean of 2 duplicates (4 values in all); error bars are 95% confidence intervals of each mean.

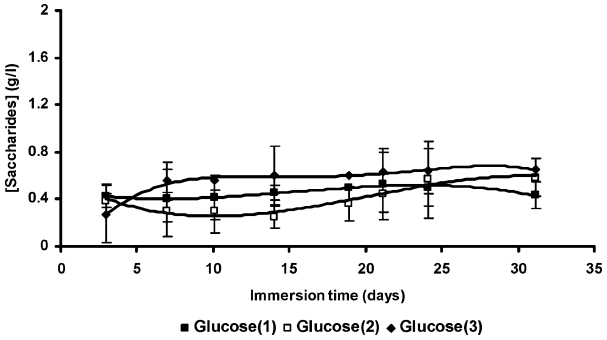

Figure 7 Concentration of glucose from HPLC in 50 ml of solution, for batch 1(■), 2(□) and 3(♦), as function of immersion time. Each value represents the mean of 2 duplicates (4 values in all); error bars are 95% confidence intervals of each mean.

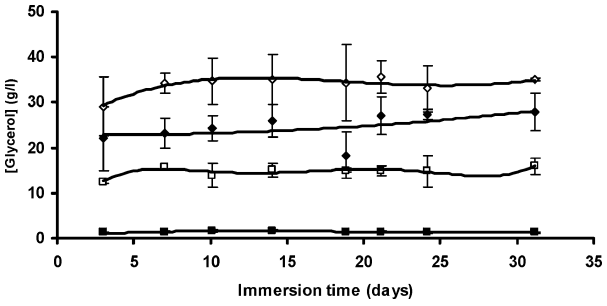

Figure 8 Concentration of glycerol in 50 ml of solution, for the 4 batches performed (□, ■, ♦, ◇), as function of immersion time. Each value represents the mean of 2 duplicates (4 values in all); error bars are 95% confidence intervals of each mean.

of the specimen's plates. Table II summarises the results obtained for D, including the 95% asymptotic confidence intervals and coefficient of determination, R^2, to account for the proportion of variation in the dependent variable. Fig. 9 shows the evolution of D with alpha values and the corresponding 95% asymptotic confidence intervals associated to the parameter estimate.

The corresponding experimental points and the curves based on the values calculated by the analytical approach previously described are plotted in Figs. 10 and 11 for the batches tested. The line is the best fit of the data to the equation describing Fick's second law of diffusion into a sheet, showing a good agreement as confirmed by the R^2 values (Table II).

TABLE II Calculated values of Diffusion coefficients of glycerol and glucose, the 95% asymptotic confidence intervals (95% C.I.) and the coefficient of determination, R^2, for four batches performed, from the non-linear fit of experimental data using the analytical approach

Batches	D_e(gly) × 10^{10} (m^2/s)	95% C.I. × 10^{11}	R^2	D_e(glu)× 10^{11} (m^2/s)	95% C.I. × 10^{10}	R^2
1	0.0659	±0.785	0.889	1.62	±1.455	0.872
2	2.10	±9.655	0.962	3.07	±0.171	0.684
3	2.89	±12.54	0.950	9.09	±0.254	0.930
4	8.08	±21.68	0.992	25.07	±0.737	0.967

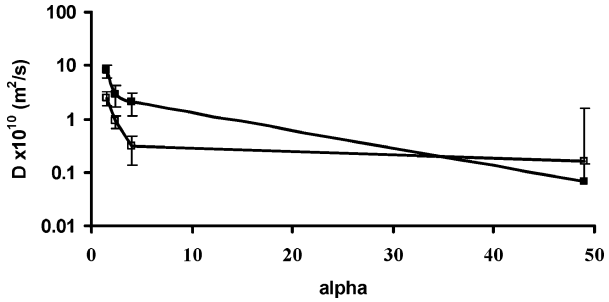

Figure 9 Values of Diffusion coefficients of glycerol (■) and glucose (□) as a function of alpha. Error bars are 95% confidence intervals on the parameter estimated.

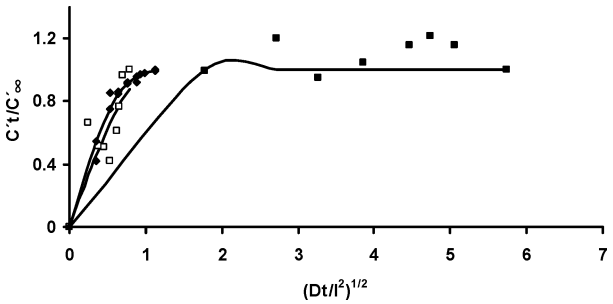

Figure 10 Dimensionless concentration ($C't/C'\infty$) of glucose versus dimensionless time ($(Dt/l^2)^{1/2}$) for batches 1(■), 2(□) and 4 (♦) as a function of immersion time. Curves were calculated from the results of the analytical (–) approach.

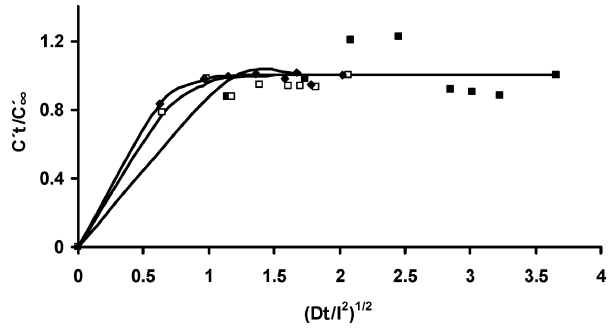

Figure 11 Dimensionless concentration ($C't/C'\infty$) of glycerol versus dimensionless time ($(Dt/l^2)^{1/2}$) for batches 1 (■), 2 (□) and 4 (♦) as a function of immersion time. Curves were calculated from the results of the analytical (–) approach.

4. Discussion

4.1. Starch in the degradation solution

In order to assess the leaching of starch from the sheet to the stirring solution, the starch in the solution was quantified in batch 1 as a function of immersion time. The results (Fig. 4) evidence a very low amount of starch in the solution. As expected the large starch molecules have difficulty to diffuse within the material, remaining inside the semicrystalline domains of the blend. The release of starch from the surface to the bulk is also limited by the low porosity of the material, and the fact that the starch molecules are strongly interspersed in the synthetic insoluble component. This interpenetrated network of starch and ethylene-vinylalcohol has reduced the rate of hydrolysis, due to presence of the ethylene copolymer in the material structure. As expected, no degradation of SEVA-C material occurs. Applying Student's *t*-test to the experimental results no significant differences were observed, being small the variation around the mean values at the 95% confidence interval.

The behaviour of the other batches with more specimens is similar, with no diffusion of starch to the solution.

4.2. Saccharides and glycerol in the solution

The three methods used to quantify the amount of reducing sugars in the solutions led to similar results: the quantity of saccharides in the solution remains invariable along the experiments, with no hydrolysis.

In order to separate and quantify all the saccharides in solution, liquid chromatography was used with a carbohydrate Ca column. With this method, only glucose and maltose were detected as saccharides in few quantities in the solution. This result was interpreted as an evidence of the difficulty of the low molecular weight fractions and small molecules to diffuse out from the inner interpenetrated domains of the blend.

To confirm the quantification of the total polysaccharides in solutions, the Dubois method was used. All the polysaccharides in solution were hydrolysed into monosaccharides, which after reaction with phenol were identified by spectophotometry. Comparing both curves (Figs. 5–7), the values are mainly due to oligomers of glucose. The curves presented a similar behaviour with the immersion time, remaining invariable during the experiments. In Fig. 4, the number of specimens increased from batches 1 to 3, the quantity of total polysaccharides also increased, as a result of low mass components that had been leached to the solution. These were confirmed by applying Student's *t*-test. The difference of the results in Figs. 6 and 7 obtained by different methods (DNS and HPLC) may be attributed to the sensitivity of the methods, giving rise different results. Nevertheless, the results obtained along the immersion time are the same, remaining invariable during the experiments. No significant differences were observed between the batches. Values are the same at the 95% confidence interval as validated by applying Student's *t*-test to the experimental results.

In the first immersion days, once the steady-state is achieved the concentration profiles are not expected to change and can give some interesting insight into the behaviour of the system.

The samples are immersed in an excess of solution and so the amount of compounds taken off by the sample will depend on the volume of "pores" which open up in the sample.

The leaching of glycerol to the solution (Fig. 8) was quantified by HPLC. The glycerol leaches quickly in the first few days of immersion, stabilizing thereafter until the end of the assay. The difference between the glycerol leached in each batch is proportional to the number of specimens in each batch, approximately. When in solution, the glycerol moves away from the material by hydrolysis, being completely soluble as it has no interaction with the copolymer. Comparing with other results already published [2], the total glycerol in the blend with one specimen, obtained by extraction is approximately 1.12 g/l, similar to the one found in batch 1. As expected, this process is followed by the material embrittlement in result of the glycerol release.

4.3. Effective diffusion coefficient for glucose, maltose and glycerol

The analytical solution of the Fick's law was applied to compute the diffusion coefficients for glycerol and glucose for the 4 batches analysed. Prediction of the diffusion process is of critical importance to understand the physics of the degradation process. Table II shows the different diffusion coefficients obtained for the two compounds, the respective 95% asymptotic confidence intervals and the coefficient of determination, R^2, to account for the proportion of variation in the dependent variable.

The changes in the diffusion coefficient along the batches are due to the alpha variable that depends directly on the material thickness. D tends to increase as alpha value decreases, since the equilibrium between the leached compounds and the liquid volume increases (Fig. 9).

According to the analytical solution of the Fick's law, the model is more accurate for smaller alpha values, as demonstrated by R^2 values ($R^2 \approx 1$). The optimization of the procedure is achieved minimizing the RSS (residual sum of squares) value that gives directly the deviation of the effective diffusion from the apparent diffusivity, improving the resulting fitting. The good agreement achieved confirms the validity of this model for the system.

The controlled pathway that is responsible for the non-diffusion is the diffusion step associated to the low porosity (approx. 0.05), because it is the slower mechanism, comparing with the enzymatic reaction rate obtained in other papers [2]. The starch diffusion from the inner regions of the blend to the bulk zone is dependent on the low porosity of the material, the rearrangement inside the blend and the transport limitation from the inner to the surface and from this to the bulk zone (inner and outer diffusion).

The compounds leached to the solution are almost only glycerol, that present greater diffusion coefficient. This plasticizer has a weak interaction with the polymer matrix, being exuded very quickly to the solution in the first immersion days. These results are in agreement with the theoretically expected, since the material degradation is difficult without enzymatic action, as demonstrated previously [2, 3].

In the present work was also possible to quantify the non-hydrolysis process, through the determination of the diffusion coefficient using an appropriate model. Figs. 10 and 11 show the respective estimations obtained for each compounds on different batches. Dimensionless variables are displayed in order to allow a comparison of the simulations with different concentrations. The data are well fitted by the theoretical predictions of equations, namely for the smaller alpha values, as demonstrated by the R^2 value (Table II).

The results on each graph display only 3 of the batches for clear observation. From a comparison of the curves, it was found that the curves are similar when the scale of the abscissa is changed.

5. Conclusions

This work validates the analysis previously presented [1] and enables to draw the following main conclusions:

– The biodegradability of starch blends is mainly related with the leaching of glycerol, other metabolites were not released. The glycerol leaches quickly in the first few days of immersion, stabilizing thereafter until the end of the assay.

– The release from the surface to the bulk can be limited by the low porosity of the material and the specific structure of this thermoplastic interpenetrated blend.

– The quantity of saccharides in the degradation solutions remains constant along the experiments and no hydrolysis occurs.

– The diffusion coefficient for glycerol tends to increase as the alpha value decreases.

– Good agreement was achieved between the calculated and measured values for smaller alpha values, indicating the validity of the model ($R^2 \approx 1$).

– It was possible to quantify the non-hydrolysis process, through the determination of the diffusion coefficient.

– The results are in accordance with the theoretically expected, since the material degradation is difficult without the action of enzymes, as was already studied in a previous work [2, 3].

– The release process is purely reaction controlled.

The optimisation of material degradability can be achieved by deliberated formed porosity in the material.

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