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# Computational modelling of extrusion process temperatures on the interactions between black soldier fly larvae protein and corn flour starch

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ABSTRACT

Insects such as the black soldier fly (BSF) are recently being studied as food sources to address concerns about how to meet the food demand of the growing world population, as conventional production lines for meat proteins are currently unsustainable sources. Studies have been conducted evaluating the use of insect proteins to produce extruded foods such as expanded snacks and meat analogues. However, this field of study is still quite new and not much has been studied beyond digestibility and growth performance. The purpose of this work was to evaluate the compatibility of protein extracted from BSF flour with corn flour starch within an extruded balanced shrimp feed model through molecular dynamics simulations, for which cohesive energy density and solubility parameter (δ) of both components were determined. The calculations' results for the protein molecule systems yielded an average δ of 14.961 $MPa^{0.5}$, while the δ for starch was calculated to be 23.166 $MPa^{0.5}$. The range of difference between both δ ($10 > \delta > 7$) suggests that the interaction of the BSF protein with corn starch is of a semi-miscible nature. These results suggest that it is possible to obtain a stable starch-protein mixture through the extrusion process.

## 1. Introduction

Protein supply is one of the most pressing challenges facing our global food demand. Already growing concerns, such as climate change and resource scarcity, have made it so most activities destined for food production are nowadays considered unsustainable. In recent years, there has been a growing interest in alternative sources of protein, based on the need to reduce meat consumption and also alleviate the cost of sources such as soy. Some of these novel sources include pulse legumes such as peas, lentils, and chickpeas (Boye et al., 2010), micro- and macroalgae (Becker, 2007), and both yeast and bacteria protein isolates (Yamada & Sgarbieri, 2005; Schoyen et al., 2007).

However, one of the most promising alternative protein sources for both food and feed is insects. Insects are generally recognized as a source of high-quality protein, as well as other macronutrients like lipids, vitamins, and minerals (Raubenheimer et al., 2014; Sánchez-Muros et al., 2014; Henry et al., 2015). Among the many species studied for this purpose, the Black Soldier Fly (BSF) shows especially interesting properties in and outside the food industry (Oluokun, 2000; Li et al., 2011; Makkar et al., 2014; Ghosh et al., 2017).

Extrusion has been extensively studied and is one of the key technologies for the utilization of insects, including BSF, in both food and feed production (Irungu et al., 2018; Smetana et al., 2018; Alam et al., 2019; García-Segovia et al., 2020). Extrusion as a process combines the operations of cooking and mixing. In this regard, proteins and polysaccharides are the most important components of food systems, since these are the main contributors to their structural and mechanical properties, primarily through the formation of gels, mainly involving

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electrostatic forces (Jamilah, 2009). In the case of starch, three possible interactions can be observed: 1) proteins penetrate and are adsorbed in the starch granule, 2) aggregation of proteins in the continuous phase, and 3) formation of covalent (and non-covalent) bonds between proteins with molecules released from starch (Rodriguez Patino & Pilosof, 2011; Kumar et al., 2017).

When preparing a mixture between two polymers, such as starch and protein, one of the main considerations to evaluate is the miscibility between components (Zhang & Thomas, 2011; Lai et al., 2017). The cohesive energy and solubility parameter are important descriptors of this property. The cohesive energy represents the total of attractive forces within a condensed state, resulting from the intermolecular interactions (electrostatic interactions, van der Waals forces, and hydrogen bridges) of the system. This cohesive energy expressed per volume unit is known as cohesive energy density (CED), it is from this CED that the solubility parameter, or Hildebrand parameter (δ) is determined (Hildebrand and Scott, 1950). These parameters are frequently used to predict the compatibility between polymers (Borton, 1991; Gupta et al., 2011). Molecular Dynamics (MD) Simulation is a technique that allows the study of interactions between molecules and how they are affected by different processes and conditions. It is a computational method designed for studying the physical movement of atoms and forcefields, based on Newtonian mechanics to understand the structure and dynamics during individual atoms' movements. Food processing operations often involve the manipulation of conditions like temperature, pressure, and pH, among others, which result in diverse properties due to interactions and molecular changes in the formed complexes. This time-dependent behaviour describes in detail the physicochemical properties of processed foods on a micro- and macro-scale (Ferrer-Gallego et al., 2016; Russo et al., 2017). This technique has already been extensively used for the design of advanced materials and pharmaceuticals (Gupta et al., 2011; Rezanka et al., 2016; Verdura et al., 2018; Zhuang, Zhang, & Liu, 2014). Its application in the food areas is still very recent and yet, it has expanded its use from small molecules to macromolecules and complex systems (Greiner et al., 2014; Feng et al., 2015; Moghaddasi et al., 2018).

MD Simulations utilising proteins and carbohydrates require several steps: preparation of the sample molecules, setup, simulation, and analysis (Fig. 1). As one of the most important carbohydrates, starch has been the object of extensive research. However, due to its large molecular size, simulations with starch are complicated and often require working with small portions and representative regions, whereas proteins get evaluated as small peptides and individual amino acids, while still obtaining satisfactory results (Bhopatkar et al., 2015; Cheng et al., 2018; Sakajiri et al., 2006; Knani et al., 2017).

The rapid advancements of current computational power and resources have enabled MD Simulations of even more complex systems, like polymer matrixes, biochemical processes, and protein interactions

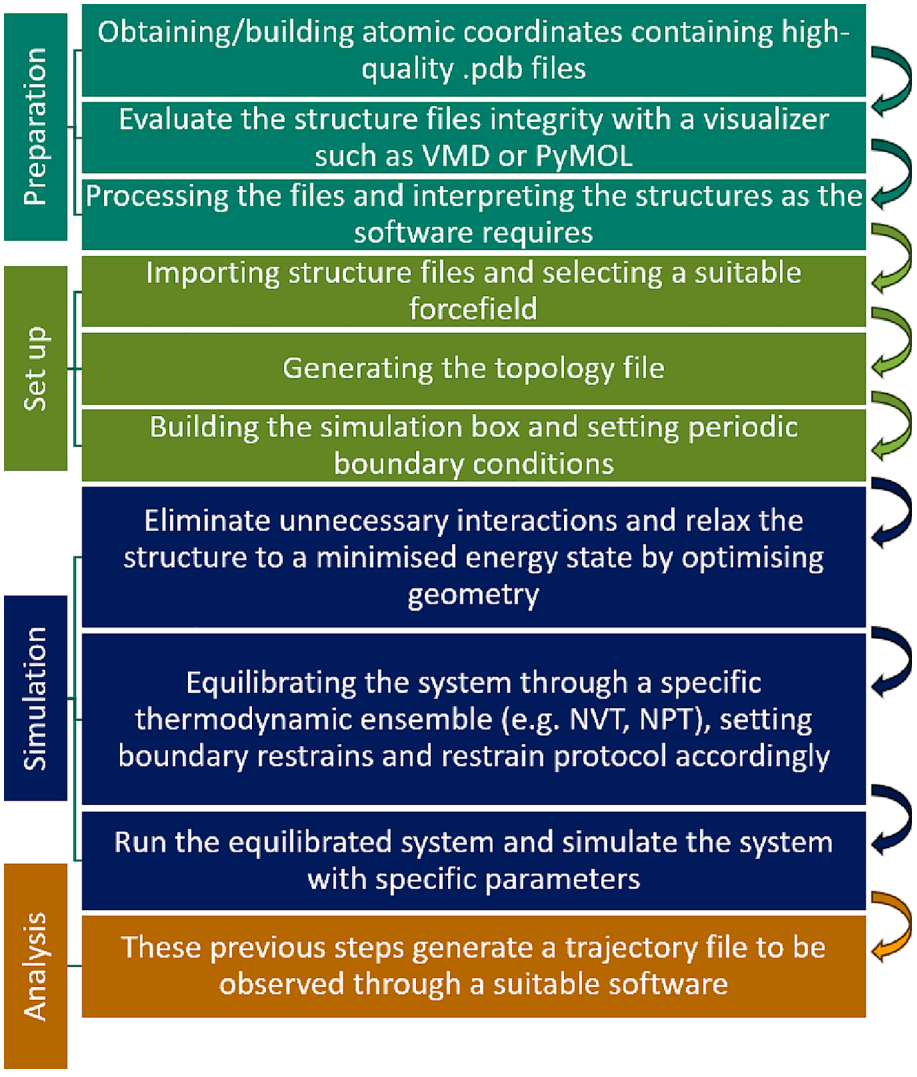


**Fig. 1.** Tasks for an MD Simulation.

(Simperler et al., 2006; Dror et al., 2012; Rakers et al., 2015), making this technique an attractive way of studying complex molecular systems, such as those products of the protein-starch interactions occurring during the extrusion process. Thus, this work aims to evaluate the compatibility of protein extracted from BSF flour with corn flour starch within an extruded balanced shrimp feed model through molecular dynamics simulation, which would lead to a better understanding of the interactions between these components in a mixed system.

## 2. Materials and methods

### 2.1. Computational tools

MD Simulations were carried out using the Materials Studio 8.0© molecular modelling package. Three simulation modules were used:

- Visualizer – it allows to draw and/or interpret molecular models.
- Amorphous Cell – a simulation tool capable of building three-dimensional periodic boundary cells.
- Forcite – a forcefield simulation tool that can perform molecular mechanics and molecular mechanics tasks. The COMPASSII forcefield was selected for this work.

### 2.2. Molecular models

For the Starch model, molecules of amylose and amylopectin were constructed from glucose monomers utilising the Visualizer module (Fig. 2). The Protein models were first extracted and characterised from a sample of dry BSF larvae previously purchased from Insekt Co., Monterrey, NL, Mexico.

#### 2.2.1. Extraction and characterisation of insect proteins.

Extraction was done following the method proposed by Yi et al. (2013), with a few adjustments. Both acid and alkaline extractions were performed. For each extraction, 400 g of previously ground larvae were suspended in 1200 mL of distilled water. pH was adjusted using mineral alkali and ascorbic acid, per the extraction route. Extracted protein was analysed through one-dimensional SDS-PAGE. For the detection of the supernatant, pellet and residue fractions, 12.5 % acrylamide gels (15–250 kDa) and 20 % acrylamide gels (2–150 kDa) were used. The applied markers were ordered from SigmaMarker (S8445, wide range, molecular weight 6.5–200 kDa SigmaMarker). The samples were dissolved in 20 mM Tris/HCl, 2 mM EDTA pH 8.0 buffers with protein concentration of 7 mg/ml and placed in an ultrasonic bath for 10 min. The protein concentration of the samples was calculated based on protein content (Dumas) and amount of dry matter. Next, protein solutions were diluted with ratio 1:1 in a sample buffer, containing 20 mM Tris/HCl, 2 mM EDTA pH 8.0 (Across Organics, Cas nr. 6381–92-6), 5 % (w/v) SDS (Sigma, Cas nr. 152–21-3), 0.016 % (w/v) DTT (DL-Dithiothreitol, Sigma, Cas nr. 3483–12-4), 0.02 % Bromophenol Blue (Merck, Cas nr. 115–39-9). Afterwards, the samples were heated at 100 °C for 5 min and centrifuged for 2 min at 10,000 rpm before applying to the gel.

Reverse-phase LC-ESI-MS/MS was used to analyse samples on the UltiMate 3000 RSLCnano coupled to the Q Exactive High Field Hybrid Quadrupole Orbitrap MS and a Nano- spray Flex ion source (Thermo Fisher Scientific). Peptides were loaded onto a trap column (300 µm ID × 5 mm, 5 µm 100 Å PepMap C18 silica), then separated on a reverse phase column (50 cm × 75 µm ID, 3 µm 100 Å PepMap C18 medium, Thermo Fisher Scientific). A data dependent top 20 method acquisition method was used with MS scan range of 400–1,600 *m/z*, resolution of 120,000 at 200 *m/z*, spray voltage of 2, AGC target of 3 × 106 and a maximum injection time of 100 ms. MS/MS scans were acquired at a resolution of 15,000 at *m/z* 200 with an ion-target value of 1 × 105 and a maximum injection of 20 ms was used (Hall & Liceaga, 2021). A total of

**Table 1**
Selected BSF proteins for simulations.

| Hypothetic Protein | Protein Mass [Da] | Relative Abundance [%] |
|---|---|---|
| A0A7R8UMF6_HERIL (HIL_P1) | 11208.65 | 13.5 % |
| A0A7R8YT67_HERIL (HIL_P2) | 22650.16 | 10.4 % |
| A0A7R8YL45_HERIL (HIL_P3) | 13229.7 | 10.1 % |
| A0A7R8UKB6_HERIL (HIL_P4) | 13367.73 | 7.6 % |
| A0A7R8YSD0_HERIL (HIL_P5) | 13488.74 | 6.8 % |
| A0A7R8ULQ9_HERIL (HIL_P6) | 11150.56 | 6.3 % |
| A0A7R8V1D0_HERIL (HIL_P7) | 13802.9 | 5.2 % |
| A0A7R8V3Y7_HERIL (HIL_P8) | 9852.93 | 4.4 % |
| A0A7R8ULW8_HERIL (HIL_P9) | 13221.52 | 2.4 % |
| A0A7R8Z1W2_HERIL (HIL_PX) | 16337.97 | 2.2 % |

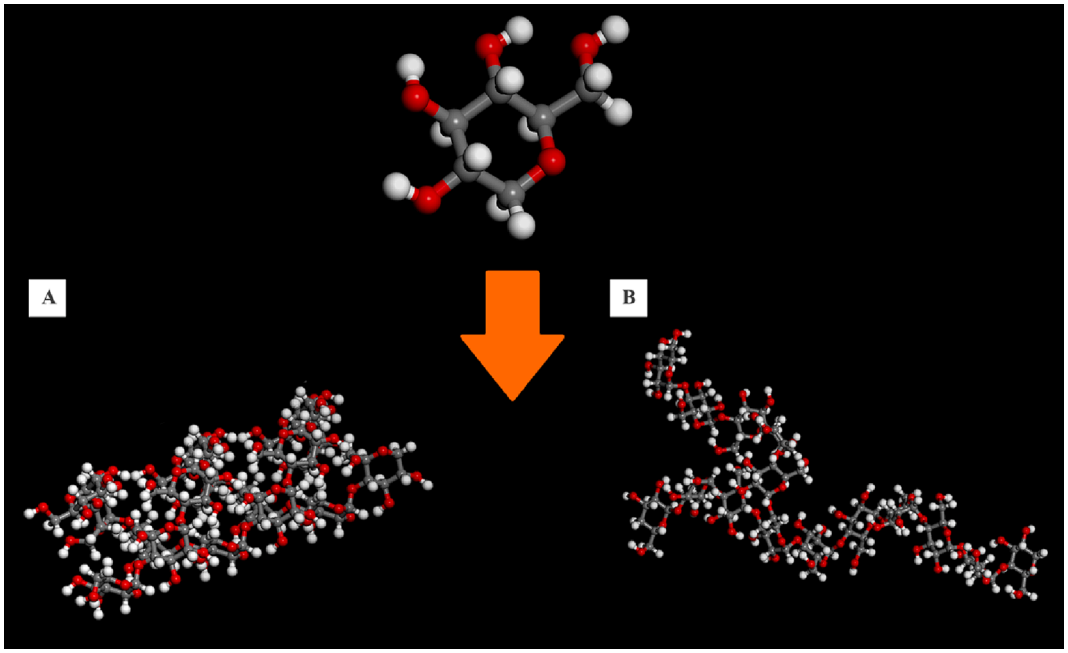


**Fig. 2.** Molecular structures of A) amylose and B) amylopectin constructed from glucose monomers.

133 proteins were identified. For this research, the 10 proteins with the highest relative abundance were selected. (Table 1). These hypothetical proteins' sequenced peptides were then matched with the Uniprot database to obtain their BLAST sequence, which was then uploaded to the I-TASSER server platform to predict the 3D molecular structure necessary for simulations (Yang et al., 2015; Roy, Kucukural & Zhang, 2010; Zhang, 2008).

### 2.3. Molecular dynamics simulation

Dynamic simulations were carried out through the following steps:

Step 1: Building the simulation cells.

Periodic boundary cells were constructed using Amorphous Cell. The Starch cell was built from fragments taken from individual amylose and amylopectin chains. This was done in order to reduce the computational load of the simulator, in this case the use periodic boundary conditions allow for a given system to be repeated upon itself indefinitely. Ten copies of the Amylopectin molecule and three of the Amylose molecule were used to most closely resemble the amylose/amylopectin ratio reported for nixtamalized corn flour (Salinas Moreno et al., 2003). Protein cells were built from each of the proteins previously predicted through I-TASSER (Fig. 3). In preparation for the simulations, these periodic boundary cells were put through a Geometry Optimization step, using the Forcite module. This consists of a minimisation of potential energy in the system Structures were optimized utilizing the Module's "smart" algorithm, (Rigby, Sun & Eichinger, 1997).

Step 2: Molecular dynamics simulation

The simulation was performed at 298 K. Each cell was subjected to three stages of simulation. First, an Equilibrium stage of 100,000 dynamic steps of 1 fs ran through an NPT (constant moles number, pressure, and temperature) ensemble. This stage was followed by a Refinement stage of another 100,000 dynamic steps of 1 fs, this time ran through an NVT (constant moles number, volume, and temperature) ensemble. Finally, a data collection stage of an additional 400,000 NVT steps was run.

All simulations were conducted on the Forcite module, using the COMPASSII forcefield. The electrostatic term was considered using Ewald and van der Waals terms using Atom-based summation methods with an accuracy of $10^{-3}$ kcal/mol. The repulsive cut-off for van der Waals term was chosen as 12.5 Å. The Nose thermostat and Berendsen barostat were chosen for the NPT MD simulations.

Step 3: Trajectory analysis.

The resulting dynamic trajectories were analysed using the Forcite module's analysis tools, calculating the following properties:

*Cohesive Energy Density (CED)*: CED is defined as the energy required to break interactions between molecules. Generally, it is measured as the heat of the vaporization of a liquid. The CED corresponds to the cohesive energy per volume unit (Maus et al., 2008). The solubility parameter δ is the measure of the capacity for materials to dissolve one another and is defined as the square root of the CED.

*Enthalpy of mixing:* CED values can be used to calculate the enthalpy of mixing (per mass unit), using Eq. (1).

$$\Delta H_m = V^{'}(\delta_1 - \delta_2)^2 \phi_1 \phi_2 \tag{1}$$

Where $\Delta H_m$ is the enthalpy of mixing (kJ/kg), V' (kg/m$^3$) is the mixture's specific volume, δ is the solubility parameter (Mpa$^{0.5}$) of substances 1 and 2, and ϕ is their volume fraction.

Enthalpy of mixing is the released (or taken-up) heat upon mixing two substances. In general terms, for a miscible phase to form between, a negative Gibbs free energy of mixing is required. Entropy change during mixing may be negligible in reactions involving polymers, and miscibility can thus be determined from the enthalpy change of mixing instead of Gibb's free energy (Sperling, 2001).

*Interaction Parameter*

Similarly, the Flory-Huggins interaction parameter χ, can be related to the Hildebrand solubility parameter δ and expressed as a function of temperature through the following equation:

$$\chi = \frac{v}{RT}(\delta_1 - \delta_2)^2 \tag{2}$$

Two criteria are usually followed when using Flory-Huggins model to assess miscibility: 1) for a miscible composition, the interaction parameter χ should be less than a critical value given by Eq. (3).

$$\chi_{cr} = \frac{1}{2} \times \left( \frac{1}{\sqrt{N_A}} + \frac{1}{\sqrt{N_B}} \right)^2 \tag{3}$$

Where $N_A$ and $N_B$ represent the degree of polymerization of the components; 2) the solubility parameters (δ) must be close enough to each

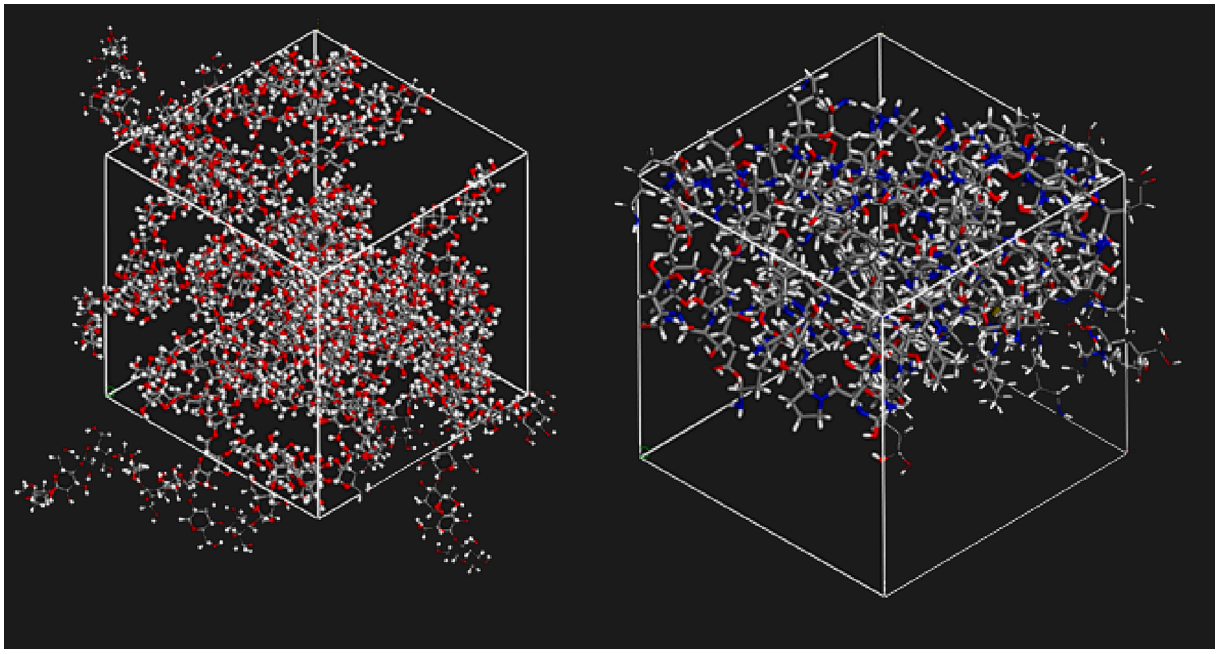

**Fig. 3.** Simulation boxes for Starch (left), and Protein HIL_P1 (right).

other since their proximity depends on the degree of favorable interaction between them. (Martinez de Arenaza et al., 2013)

## 3. Results

### 3.1. Extraction and characterisation of insect proteins

Out of the ten selected proteins, eight were identified as having a 35–36 amino acid sequence motif, known as the R&R consensus. The presence of this region suggests that these proteins have the function of binding chitin. These chitin-binding proteins amount to 62.2 % of the protein content of the larvae. The cuticle of insects is composed of proteins and chitin. The type of cuticular protein is usually specific to the type of cuticle (rigid or flexible), which itself is specific to the insect's life stage. This region is most commonly present in proteins forming the soft cuticle of larvae and pupae, which is expected with the proteins being extracted from the larval stage (Rebers & Riddiford, 1988; Rebers & Willis, 2001).

### 3.2. Cohesive energy density

The constructed cells were subjected to a series of geometry optimization steps to obtain a minimum state of potential energy and efficient packing of the molecules in the cell (Fig. 4). This was achieved by the use of the Forcite's module "smart" algorithm, which consists of a cascade of optimization algorithms going from steepest descents methods to Fletcher-Reeves conjugate gradients to remove unfavourable interactions and attain the lowest energy state. The time to reach equilibrium depends on the size of the system, therefore, simulations in the equilibrium stage were carried out until a stable energy profile was obtained. The time evolution profiles for the simulated cells indicate the time selected (600 ps) was adequate for equilibrium (Fig. 5). Density, CED, and solubility parameter (δ) were calculated for starch and all insect proteins (Table 2), Starch density is in reasonable agreement (96 %) with reported values for corn starch (Ibrahim et al., 2019). Fischer et al. (2004) determined protein density to be a molecular-weight-dependent property, with a positive deviation from the generally accepted value of 1.35 g/cm$^3$, particularly in proteins with low molecular weight (M < 30 kDa), exhibiting densities from 1.42 to 1.48 g/cm$^3$ within the 8–25 kDa molecular weight, as is the case with the densities calculated for BSF proteins.

It's been established that compounds with similar δ values are thermodynamically compatible, and thus, are miscible. Polymer blends are usually classified into three categories: miscible, semi-miscible, and immiscible, depending on molecular weight and the structure of the components. Generally speaking, this depends on the value of $\Delta G_m$, given by

$$\Delta G_m = \Delta H_m - T\Delta S_m$$

where $\Delta G_m$ is the Gibbs free energy of mixing, $\Delta S_m$ is the entropy factor and is a measure of disorder or randomness, is always positive and, therefore, is favourable for mixing, especially in low-molecular-weight mixtures. In contrast, polymer mixtures have high molecular weights and thus are decided by the enthalpy of mixing $\Delta H_m$, where exothermic mixing is driven towards miscibility (Flory, 1953).

In terms of the solubility parameters, this distinction is given by the difference between values of δ: compounds with $\Delta\delta < 7.0$ MPa$^{0.5}$ tend to be miscible, while $\Delta\delta > 10.0$ MPa$^{0.5}$ is usually an indicator of an immiscible system (Greenhalgh et al., 1999).

The difference in δ values of starch and insect proteins indicates that, on average, the interaction between the molecules is that of a semi-miscible system. This was attributed to the fact that several of these proteins were identified as cuticle proteins, specifically chitin-binding proteins. In insects, the cuticle is a product of the chitin fibres interacting with cuticular proteins (van Huis et al., 2015); for these interactions to take place, cuticle proteins ought to have a chemical structure with a high affinity to chitin. To corroborate this, the same set of simulation steps was performed on a cell constructed from five chitin octamers. This chitin system had a calculated δ of 17.859 ± 0.023; the close similarity between this value of δ and those of the proteins is a clear indication of a thermodynamically compatible system (Forster et al., 2001).

### 3.3. Miscibility and chi interaction parameter

$\chi_{cr}$ was calculated to have a value ranging from 0.009485 for the most favourable starch-protein interaction to 0.015676 for the least favourable interaction, averaging 0.013002 across the ten selected proteins. Average χ for the starch interaction with insect proteins was calculated to be approximately 0.0275 at the software's initial temperature of 298 K; this χ value, however, will tend to decrease as temperature rises, reaching a value of 0.01939 at 423 K, corresponding to the 150 °C commonly utilised in extrusion processes of food products. While this value is still greater than $\chi_{cr}$, suggesting this starch-protein interaction is in fact not miscible, a small value of χ is generally an indicator of miscibility in a binary system (Flory, 1953; Martinez de Arenaza et al.,

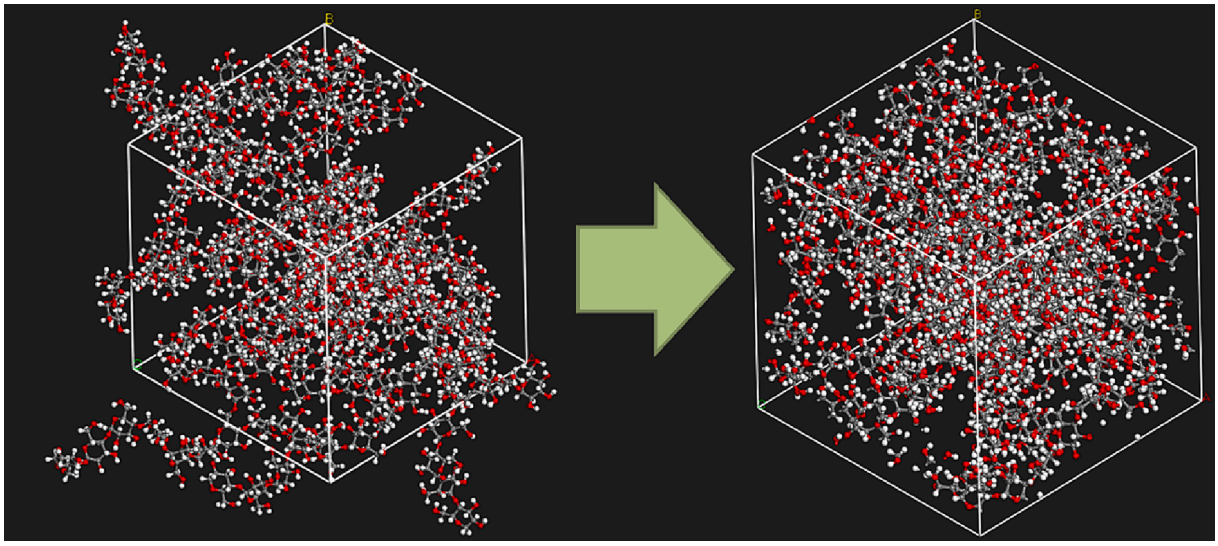

**Fig. 4.** Energy minimized structure of starch: $E_{initial}$ = 5453.68 kcal/mol, $E_{final}$ = 5165.86 kcal/mol.

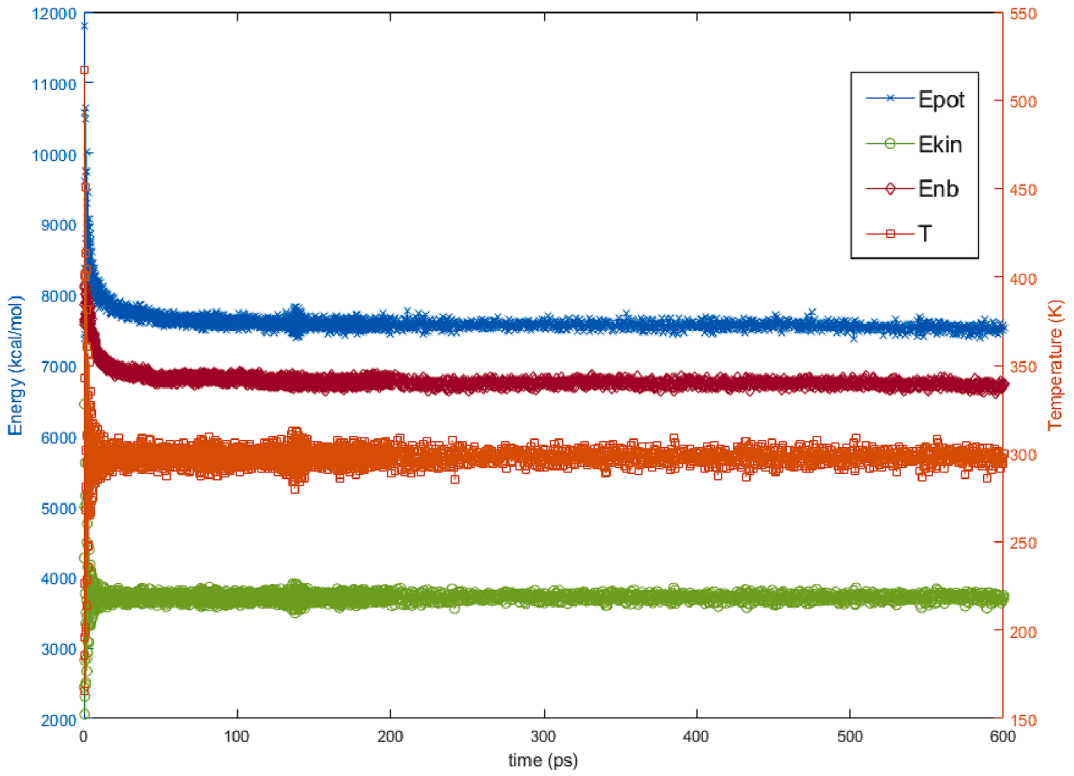


**Fig. 5.** Plot of the total potential energy (Epot), non-bonded energy (Enb), kinetic energy (Ekin), and Temperature (T) for starch as a function of MD Simulation time.

**Table 2**
Density, CED, and Solubility parameters calculated during the simulation.

| Compound | CED (MPa) | δ ($MPa^{0.5}$) | Density ($g/cm^3$) |
|---|---|---|---|
| Starch | 537.1 ± 2.58 | 23.166 ± 0.061 | 1.301 |
| HILP1 | 258.9 ± 1.79 | 16.076 ± 0.060 | 1.471 |
| HILP2 | 277.5 ± 1.55 | 16.650 ± 0.050 | 1.435 |
| HILP3 | 192.2 ± 0.82 | 13.860 ± 0.031 | 1.462 |
| HILP4 | 213.7 ± 1.28 | 14.609 ± 0.049 | 1.462 |
| HILP5 | 204.0 ± 1.06 | 14.277 ± 0.040 | 1.461 |
| HILP6 | 201.0 ± 1.16 | 14.168 ± 0.044 | 1.471 |
| HILP7 | 201.4 ± 0.82 | 14.188 ± 0.030 | 1.460 |
| HILP8 | 237.9 ± 1.15 | 15.417 ± 0.039 | 1.478 |
| HILP9 | 206.3 ± 0.94 | 14.359 ± 0.035 | 1.462 |
| HILPX | 256.9 ± 1.81 | 16.011 ± 0.067 | 1.453 |

2013). Thus, semimiscibility can be expected for this system.

By applying the obtained values of δ to the enthalpy of the mixing equation, it was determined that, on average, a minimum of 13.67 kJ/kg are necessary for the system to show favourable mixing interactions. This relatively low energy requirement may be satisfied by the extruder through its Specific Mechanical Energy (SME) input. This is defined as the energy going into the extrusion system per unit mass as work from the motor. This energy is passed into the extrudate by viscous dissipation and is then converted primarily into heat (Riaz, 2000).

## 4. Conclusions

In this research, MD Simulation methods were successfully used to measure the cohesive energy density and solubility parameter for systems corresponding to a starch model and ten Protein models extracted from BSF larvae. The resulting density calculations are in agreement with values reported in the literature, suggesting an effective optimisation of intermolecular interactions and thus, packing of the simulation cells. It was predicted by MD simulations that interactions between starch from corn flour and protein extracted from BSF larvae would be semi-miscible. This was attributed to the proteins' characteristics which make them compatible with chitin, which as an insoluble fibre, also presents poor interaction capabilities with carbohydrates, including starch. This semi-miscibility is also denoted by a relatively low energy requirement to favour a state of mixing, which could be satisfied by the extrusion process.

The use of MD simulations can provide insight into the molecular level of the mechanisms and energy contributions of a given system, aiding in the development of more robust food and feed formulations. This technique has the potential application for selecting lead ingredients during the development of new products while minimising the need for extensive physical assessment studies.

## CRediT authorship contribution statement

**Jorge Iñaki Gamero-Barraza:** Writing – original draft, Software, Methodology, Investigation. **Gerardo Antonio Pámanes-Carrasco:** Formal analysis. **Efrén Delgado:** Funding acquisition, Formal analysis. **Cristian Patricia Cabrales-Arellano:** Methodology, Investigation, Data curation. **Hiram Medrano-Roldán:** Visualization, Resources, Conceptualization. **Daniela Gallegos-Ibáñez:** Resources, Conceptualization. **Harald Wedwitschka:** Resources, Conceptualization. **Damián Reyes-Jáquez:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fochms.2024.100202.

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