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MICROSTRUCTURED DRUG-DELIVERY SYSTEMS AS SOLID DISPERSIONS USING PEG 6000 AND POLYSORBATE 80 CONTAINING HYDROCHLOROTHIAZIDE: development, synthesis, and physicochemical and morphological characterization

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ABSTRACT

Bioavailability indicates the speed of dissolution and absorption of the drug by its active site, characterization of the potential pharmacological effect, dosage of a medication, and the effectiveness of treatment. Microstructured systems make it possible to increase the efficiency of drug release and absorption processes that have low solubility in physiological media and are extremely important in the area of drug development and new pharmaceutical forms. The drug containing hydrochlorothiazide, distributed by RENAME and widely used for the treatment of arterial hypertension is classified as poorly permeable and poorly soluble, thus having low absorption and bioavailability, which requires administration of high doses to generate side effects. and lack of treatment adherence. The application of a microstructured drug-delivery system in the form of a solid dispersion containing hydrochlorothiazide, a lipophilic drug, dispersed in a solid matrix found by the hydrophilic carriers PEG 6000 (polyethylene glycol) and polysorbate80, given the increased solubility, dissolution profile and consequently the bioavailability of the drug. The system was extended physically-chemically and morphologically utilizing testicles such as scanning electron microscopy (SEM), in addition to thermogravimetry (TGA), differential scanning calorimetry (DSC), and infrared absorption spectroscopy, with satisfactory results in that region. formation of an efficient and innovative drug delivery system.

Keywords: Solid dispersion, PEG 6000 (Polyethyleneglycol) and hydrochlorothiazide.

1. INTRODUCTION

Hydrochlorothiazide is a thiazide diuretic used in the first-line treatment of high blood pressure, listed as an essential drug on the WHO list. However, it belongs to class IV,of drugs of the Biopharmaceutical Classification System (BCS), which orders drug classes from I to IV, considering their solubility and permeability constants in a decreasing way, that, is hydrochlorothiazide stands out for presenting the lowest levels of solubility, permeability, and bioavailability among all drug classes. With low bioavailability,

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there is a significant loss of therapeutic efficacy. Thus, it requires a compatible and efficient administration system (drug-delivery system) (KUMAR et al., 2018).

Bioavailability is defined as the fraction of the active form of a drug that reaches the systemic circulation, that is, the extent to which a substance becomes completely available for biological fate. The route of administration characterizes the dosage of a drug, as it guides its pharmacokinetics, due to the modification of the serum concentration caused by intestinal absorption or first-pass metabolism, which occurs in the oral drug, but not in the intravenous since its administration immediately delivers the drug. drug to the systemic circulation. The dose is indirectly proportional to its bioavailability, that is, a drug with relatively low bioavailability requires a higher dose to exceed the lower concentration limit and obtain a therapeutic effect (PATEL; PRICE, 2020).

Several studies have been developed to propose a pharmaceutical form that maximizes the bioavailability and actions of hydrochlorothiazide and simultaneously improves adherence to treatment by patients, by allowing a decrease in the administered dose (DE SOUZA et al., 2017). High bioavailability can reduce dosage and side effects for the patient (DOBROWOLSKI et al., 2019).

Systems such as nanocrystals, complexation, self-micro (nano) emulsification, emulsification, co-crystals, and solid dispersion drug delivery systems are being used to enhance the solubility and dissolution of drugs. The latter is widely used through synthesis methods such as melting, solvent evaporation, spray drying, supercritical anti-solvent process, and lyophilization (CHOI et al., 2018).

To break the limitations of conventional drugs, new technologies, such as the use of carriers in drug formulation, aim to improve drug solubility, absorption, permeation, retention in target tissues, bioavailability, circulation time, and stability, moreover, they can protect various drug molecules against premature degradation in the body and show greater absorption efficiency in target cells compared to normal cells. Studies of this type are of great importance, since 90% of the drugs on the market are hydrophobic or poorly soluble in water, to restrict the delivery of the drug to the systemic circulation (RANJOUS et al., 2019).

The technique used is constituted by the dispersion of a pharmacologically active component in a biologically inert matrix (carrier), constituted by polymers, which can be associated with surfactants (to adapt the physicochemical properties of the polymers to the dispersion system and increase its stability), excipients used in the preparation include propylene glycol (PG), polyethylene glycol (PEG) 4000, 6000, and 8000, Polysorbate-80, and povidone (PVPK-30). Its application translates into increased wettability and porosity, greater uniformity of the contact surface, a significant reduction in particle size, possibly at the molecular level, change from crystalline to amorphous state, providing greater solubility and higher dissolution rates, observing improvement of therapeutic action due to increased bioavailability (DE SOUZA et al., 2017).

This work aimed to develop microstructured systems through the application of solid dispersions containing the drug hydrochlorothiazide and a solid matrix consisting of PEG 6000 (polyethylene glycol) and polysorbate 80, in addition to its physicochemical and morphological characterization.

2. THEORETICAL REFERENCE

Medicines act in the prevention, relief of symptoms, and cure and diagnosis of diseases. Developed with strict technical inspection, in pharmacies or industries, so that the research, production, and commercialization stages can satisfy the criteria determined by ANVISA. They may have different pharmaceutical forms, such as capsules; pills; powders; sprinkles; solutions, among others, to guarantee the patient's adherence to the treatment, protect the substance during its journey through the body, guarantee the precision of the dose and the presence of the drug at its site of action. The drug effects are due to one or more active principles with scientifically recognized therapeutic properties (ANVISA, 2010).

The absorption, bioavailability, and pharmacokinetic profile of drugs are widely discussed in the pharmaceutical field. The biopharmaceutical classification system (SCB) classifies drugs according to their solubility and permeability. Class I has drugs with high solubility and permeability (84% of drugs); class II contains poorly soluble and highly permeable (17%); class III with highly soluble and poorly permeable (39%); and class IV, poorly soluble and permeable (6%) (JATWANI et al., 2012). Research in pharmaceutical technology addresses physical modifications focused on the generation of amorphous states and particle size reduction, to increase the degree of dissolution of poorly soluble active ingredients, in addition to the surface area, particle wettability, and solubility. (GOMES et al., 2015).

Observing that poorly water-soluble drugs with reduced dissolution rate are affected by the pharmaceutical form or by the release system, the use of the solid dispersion system (DS) is chosen, characterized by the incorporation of a drug in a hydrophilic carrier polymer (LACERDA; LIONZO, 2011). The technique provides significant advantages, such as increased wettability, reduction in particle size, possibly at the molecular level, porosity, increased contact surface, uniformity, and change from crystalline to amorphous state (DE SOUZA et al., 2017).

Using DS, microparticles are formed, allowing the greater dissolution of conventional formulations, such as capsules and tablets. The act of transforming the drug from the crystalline state to the amorphous state improves solubility, as it facilitates its contact with the dissolution medium. The solvation energy in the dissolution process is reduced due to the conformation of the molecules that allow the increase of aqueous solubilization in the amorphous state (LARIZA et al., 2012).

The technique has a low cost, being accessible to laboratories. Although few drugs on the market use the technology, it has been studied for more than half a century, innovation in its use is observed, and scientific articles, equipment, and carriers have emerged (SIMÕES, 2015). The drugs GrisPEG®, Sporanox®,

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and Kaletra® are examples of pharmaceutical specialties on the market, obtained by solid dispersion technology. This information is represented in Table 1, adapted from the New Jersey Center for Biomaterials (2015).

Table 1 - Examples of Medicines (Pharmaceutical Specialties) with Solid Dispersion Technology.

Medicines	Drugs	carriers	Method	Year of Approval	Industry
GrisPEG ®	Griseofulvin	PVP, PEG 400 and 8000	hot melt	1975	Pedinol Pharm Inc.
Sporanox ®	Itraconazole	PEG	Spray Drying	1996	Jansen
Kaletra ®	Lopinavir/RItonavir	PVP and PEG	hot extrusion	2005	Abbott

Source: Adapted from “New Jersey Center for Biomaterials”, 2015.

Fusion, fusion-solvent and kneading, supercritical fluid, and spray drying are cited as methods of obtaining DS, commonly used (ALVES, 2010). In the fusion-solvent method, the drug is dissolved, and the carrier is added to a solvent, which will then be evaporated by rotary evaporation, spray-drying, or vacuum drying. In the spray-drying method, the solvent is evaporated by rapid drying. The supercritical fluid uses extraction equipment in the supercritical state and by the action of CO2 the solvent is extracted from the dispersion, it does not use high temperatures. Malaxing is formed by mixing the drug, cyclodextrins (compounds that have a hydrophobic center and a hydrophilic surface), and a small amount of water, using the geometric dilution method. The mixture is kneaded and oven dried (STORPIRTIS et al., 2011). DS has different generations (Table 2) according to the characteristics of the carriers and their composition.

Table 2 - Carrier characteristics as a function of generations of solid dispersions.

Generations	Carrier characteristics	Composition example
First generation	crystalline carriers	urea and mannitol
Second Generation	polymeric carriers	PVP, PEG, HPMC, HPC e polimetacrílico
Third Generation	Blend of surfactants and polymers	Poloxamer® 407 and polysorbate
Fourth Generation	Water insoluble polymers	ethylcellulose, carbomer or carboxylimic polymer.

Source: Adapted from CID et al., 2019.

The third generation generally employs polysorbate 80 and polyethylene glycol carriers. According to the sixth edition of the Brazilian Pharmacopoeia (2019), the first is described as a surfactant, nonionic, solubilizing, emulsifying, and wetting agent, it can also be found in different forms, such as polysorbate 20, polysorbate 40, polysorbate 60 and polysorbate 80, each having different characteristics. Polysorbate 80 is a clear, viscous liquid with a light brown or yellowish color, a characteristic odor, and a slightly bitter taste, it is miscible in water, ethyl acetate, and absolute ethanol, and practically insoluble in liquid paraffin and fixed oils.

Polyethylene glycol 6000, on the other hand, is a synthetic polymer, it has high molecular weight, polymer chain flexibility, capable of forming hydrogen bonds and dispersing in water. Thus, an inert solid matrix prevents the development of liposoluble drug crystals, increases their concentration in the body, and, therefore, their bioavailability. (VILLANOVA; ORÉFICE; CUNHA, 2010). PEG is applied to the solid dispersion method, mainly in the second generation, decreasing the crystallinity of drugs using a carrier. It can also be used to obtain solid dispersions, solid solutions, or physical mixtures, with the aim of this work being the formation of solid dispersions containing hydrochlorothiazide (VARGAS, 2014).

The use of surfactants in solid dispersion is mainly seen in third-generation microstructures. The use of a hydrophilic polymer together with a surfactant is a recurrent strategy in several researches, an example of the practice is the use of polyethylene glycol with polysorbate 80. Surfactants used as carriers can prevent the recrystallization of the drug, by stabilizing the dispersion solid (ELOY, 2012). According to the BCS, hydrochlorothiazide belongs to biopharmaceutical class IV, that is, it is characterized by low permeability and solubility. Physicochemical and biopharmacotechnical properties will interfere with the bioavailability of the drug after its oral administration. The solubilization in the gastrointestinal fluids, followed by the permeability of the active ingredient through biological barriers, is essential to reach the site of action, therefore, the control or modulation of the biopharmaceutical properties of class IV drugs like this one, makes possible the improvement of its oral absorption and, consequently, may lead to a decrease in the administered dose (MENDES, 2016).

According to the Brazilian Pharmacopoeia (2019), hydrochlorothiazide or 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide is described as a diuretic therapeutic class. It is a white or almost white, odorless crystalline powder. It is sparingly soluble in water, sparingly soluble in ethanol, soluble in acetone, and in dilute solutions of alkali hydroxides.

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It has a melting range of 266 to 270ºC, with decomposition. According to the package insert for pharmaceutical specialties, the use of the drug aims to eliminate liquids from the body through urine. Its effect begins 2 hours after its administration, however, during the first to second and a half hours, the maximum plasma concentration is reached, and its action lasts for 6 to 12 hours. The composition of the tablet consists of 50 mg of hydrochlorothiazide and the excipients used are starch, silicon dioxide, microcrystalline cellulose, magnesium stearate, and talc.

Considering that the most common cardiovascular disease is systemic arterial hypertension, in addition to having an increase in its prevalence with age, about 50% of people over 60 years of age are hypertensive patients (CHOBANIAN et al., 2003). Left ventricular hypertrophy and pathological changes in vascularization are caused by high blood pressure, representing the main cause of stroke, being a risk factor for coronary artery disease and its complications, that is, heart failure and dissecting aortic aneurysm contribute to infarction. cardiac arrest and sudden cardiac death (KATZUNG, 2003).

3 METHODOLOGY

The solid dispersion was manipulated through the solvent fusion method, in which the drug and the microcarriers used, polysorbate 80 and PEG 6000, were solubilized in a common organic solvent, and then the solvent was evaporated under constant stirring, using a rotary evaporator, resulting in a solid, dry residue. This solid was kept in a desiccator until the weight remained constant and, later, it was pulverized (ALMEIDA, 2009).

Amid the complexities of the project, through the syntheses carried out by the rotary evaporator and vacuum drying, the first attempts to form a solid dispersion of hydrochlorothiazide containing polysorbate did not show satisfactory results. Thus, through studies, the excipient PEG 6000 was used, thus improving the quality of the dispersion formed.

3.1 PREPARING THE MICROCARRIER IN THE FORM OF SOLID DISPERSION

PEG 6000 and Polysorbate 80 were used as hydrophilic carriers in this synthesis and acetone was used as an organic solvent.

An amount og 20g of PEG 6000, 2g of hydrochlorothiazide, and 2g of Polysorbate were weighed, and the volume of acetone (30 ml) was also measured. The HCTZ and the polysorbate were dissolved in acetone, and in parallel, the PEG 6000 was melted in a water bath. The drug-containing solution was poured slowly, under vigorous stirring, into the PEG 6000. The system formed was transferred to a round bottom flask. The rotaevaporator was used (Figure 1), using the solid dispersion method “fusion-solvent”, to allow the fusion of the microcarrier, homogenization of the formed system, and elimination of the organic solvent, due to the heat and high volatility of acetone.

Figure 1: Preparation of the solid dispersion.

Source: The authors, 2020.

After cooling and solidification, the material formed was removed from the flask by scraping and homogenized by spraying, with the aid of a mortar and porcelain pestle. The white dispersion (without the drug) was performed in the same way as the DS containing the drug.

Figure 2: Solid dispersion containing the drug before being sprayed.

Source: The authors, 2020.

3.2 PHYSICO-CHEMICAL AND MORPHOLOGICAL CHARACTERIZATION OF THE STUDY STRUCTURES

The evaluation of the interaction between the solid dispersion and the drug is necessary to know the level of interaction between the participants of the studied dispersion (VARGAS, 2014). It is characterized through the analysis of absorption spectroscopy in the infrared region; differential scanning calorimetry; thermogravimetry and scanning electron microscopy.

3.2.1 ABSORPTION SPECTROSCOPY IN THE INFRARED REGION (FTIR)

A technique performed through the irradiation of infrared rays

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in the sample, stimulating the emission of vibrational and rotational transmissions, then the Vibro-rotational deformation is measured, determined by the energy levels and shape of the molecule that constitute the substance. The analysis is based on the fact that different chemical bonds show specific frequencies that vibrate at fixed energy levels. When a drug is characterized by low water solubility and interacts with a water-soluble microcarrier, hydrogen or Van Der Walls bonds are formed. These are weak bonds that emit Vibro-rotational deformations that are visualized by IR spectrometry (LIRA, 2004).

To read the spectrum, the samples were transformed into KBr pellets, after which the KBr was dried, with FTIR purity: with the aid of a porcelain crucible in a muffle furnace at 600°C for 4h. An amount of 0.8g of dry and desiccated KBr and 0.2g of dry sample were ground with the aid of a mortar and an agate pestle. The powder was transferred to the die and punches set for cold pressing with a uniaxial press and thus the tablet was removed using the apparatus for extrusion and transfer to the appropriate support; the results were analyzed from the construction and plotting of graphs of the analysis reading through the OriginPro8® program.

3.2.2 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Measures the difference in energy provided by a substance or mixture to reference material, according to temperature, obtaining quantitative data on decomposition, oxidation-reduction, dehydration, and changes in physical state (SILVA; PAOLA; MATOS, 2007). It can determine enthalpy, dehydration, purity, drug/excipient affinity, and polymorphism, and can be used to assess the thermal stability of hydrochlorothiazide in solid dispersion (STORPIRTIS et al., 2011).

The curves were obtained using the Thermal Analysis sdt q600 device, under a dynamic nitrogen atmosphere (flow of 50 mL min 1), in the temperature range from 25 to 600°C, using hermetically sealed aluminum capsules, with a mass of approximately 2.0 mg, heating rate 10°C/min. The results were analyzed in the OriginPro 8® program.

3.2.3 THERMOGRAVIMETRY (TG)

It evaluates the sample's mass variation as a function of temperature, allowing it to verify the thermal stability of a drug and/or a microcarrier, through the temperature range in which the material does not change its mass (STORPIRTIS et al., 2011).

The curves were obtained using the Thermal Analysis sdt q600 apparatus, under a dynamic nitrogen atmosphere with a flow rate of 50 mL min 1, in the temperature range from 25 to 600°C, using hermetically sealed aluminum capsules with a mass of approximately 2.0 mg of sample, the heating rate of 10°C/min with an inert atmosphere of nitrogen.

3.2.4 SCANNING ELECTRON MICROSCOPY (SEM)

Performed through a microscope capable of allowing the visualization of high-quality topographic images of the three-dimensional and microstructural particularities of solid objects (DEDAVID et al., 2007).

The samples were transferred to a sample holder with carbon glue and then gold deposition was carried out through plasma. Finally, the samples were analyzed in an SEM device, Jeol., model JSM 6510.

4 RESULT AND DISCUSSION

4.1 ABSORPTION SPECTROSCOPY IN THE INFRARED REGION (FTIR)

The absorption spectra in the infrared region of the synthesis were obtained by the vibrational spectrum device (Figure 3), performed in the region of 4000-500cm-1, at room temperature. The samples were applied over the horizontal attenuated total reflectance (ATR) fixture**.**

Figure 3: Vibrational Spectrometer Device.

Source: The authors.

From the transmittance/wavelength graphs, Figure 5 (A and B) was constructed to facilitate the interpretation of the results, presenting the variations in the curves, so that the differences between the formed systems and the pure substances can be visualized more easily.

Analyzing the graph of the solid dispersion containing the drug (Figure 5, red line), there are no characteristic peaks of the solvent used during the preparation of the solid dispersion, that is, the peak 1531 , characteristic of alkenes (C=O) function present in the acetone molecule, It is concluded that, as the solvent is highly volatile, it must have been evaporated in the rotary evaporation process, leaving no interfering residues and suggesting that the drug was correctly dispersed to its PEG carrier 6000. There was no residual solvent (acetone) in the complete dispersion, this was evaporated during the synthesis process by the rotary evaporator, an important fact, since acetone is not physiologically inert.

Comparing the complete solid dispersion graph (Figure 5, blue

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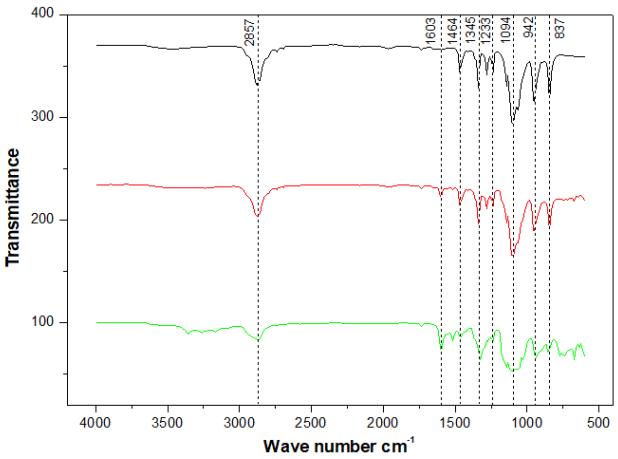
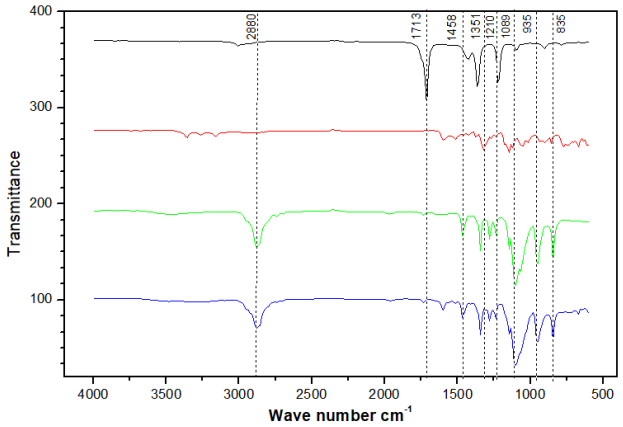
line) and the graph of the drug hydrochlorothiazide (Figure 5, red line) it is possible to verify that there are no characteristic peaks of the functional groups of the drug (amines present in the 1713 , 1351 , and 1210 bands) therefore, due to the absence of characteristic bands of the drug in the complete solid scatter plot, it is concluded that the drug has been fully incorporated within the solid dispersion.

Figure 4: Infrared spectra of the samples.



Caption: White solid dispersion (without the active Hydrochlorothiazide) (black line); Solid dispersion containing hydrochlorothiazide (red line); Physical blend containing PEG6000, Polysorbate 80 and Hydrochlorothiazide. **Source:** The Authors.

Figure 5: Infrared spectra of samples.



Caption to photos 4 and 5: IVH: Hydrochlorothiazide; IVDSH: Solid dispersion with hydrochlorothiazide; IVDSB: white solid dispersion; IVPPH: Physical mixture (1:1) of PEG 6000, polysorbate 80 and hydrochlorothiazide; IVPH: PEG 6000+ hydrochlorothiazide physical mixture; acetone = acetone. **Source:** The authors.

Table 3: Wavenumber and type of interaction.

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Source: The authors.

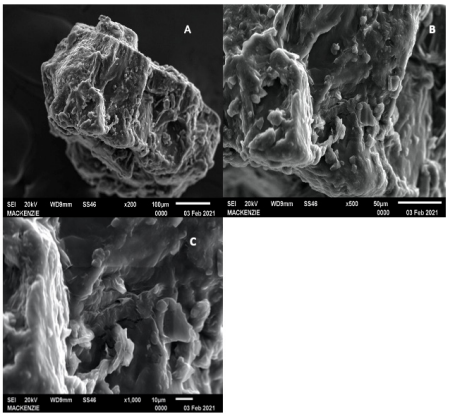
Bands observed in the white solid dispersion (figure 5, green line) are similar to those of the dispersion containing hydrochlorothiazide (figure 5 blue line), remembering that the white dispersion does not contain the drug hydrochlorothiazide and that the characteristic peaks of the drug are not present in the graph of complete solid dispersion, contemplates the justification that the drug was incorporated into the complete solid dispersion.

When analyzing the graph of the physical mixture containing hydrochlorothiazide, polysorbate 80, PEG 6000 and acetone (Figure 4 black line) we verified an enlargement of the 1094 band, the main difference comparing the peaks present in the complete solid dispersion. The 1094 band corresponds to the aliphatic amine bond, characteristic of acetone. Thus, as the solid mixture did not undergo the rota-evaporation process, it is possible to notice the broadened band corresponding to the functional group of acetone, due to the rota-evaporation process that the complete solid dispersion underwent, we did not verify such band stretching.

4.2 SCANNING ELECTRON MICROSCOPY (SEM)

Observing the morphological aspects of the SEM PEG 6000 images, they show that this material does not present fragments on its surface. It is possible to notice the presence of several granules spread over the surface. As the image's magnitude is increased, some roughness is noticed in the material (Figure 6).

Figure 6: Analysis of PEG6000 at different image magnitudes.



(A) PEG sample at 200x magnification; (B) PEG 6000 sample at 600x magnification; (C) PEG 6000 sample at 1000x magnification. **Source:** The authors.

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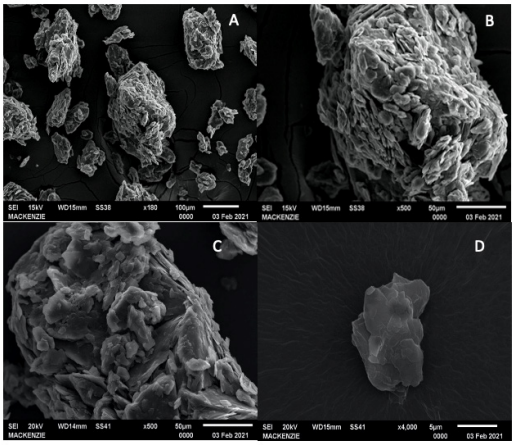
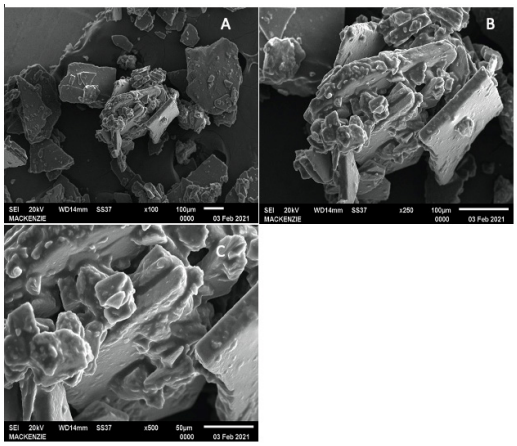
Figure 7: Analysis of white solid scattering at different image magnitudes.



(A) White solid scatter at 180x magnification; (B) White solid scatter at 500x magnification; (C) White solid scatter at 500x magnification; (D) White solid scatter at 4000x magnification. **Source:** The authors.

Observing the images of the white solid dispersion (figure 7), we can see several particles and fragments of the material, which have a scaly surface composed of small, agglomerated fragments. However, when analyzing an isolated particle, a noticeable difference is noticed on its surface, giving rise to a lamellar appearance, formed by overlapping fragments.

Figure 8: Analysis of the solid mixture containing Polysorbate 80+ PEG 6000+ Hydrochlorothiazide at different image magnitudes.

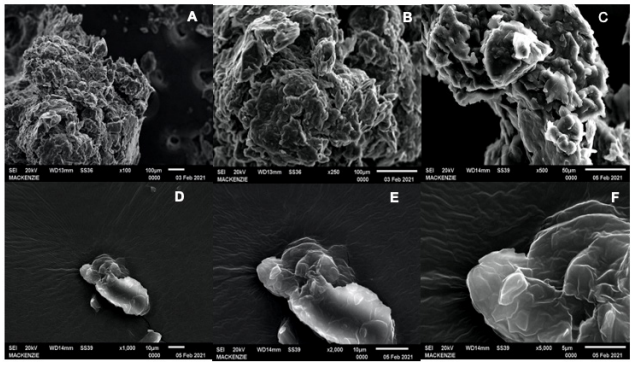


(A) solid mixture at 100x magnification; (B) solid mixture at 250x magnification; (C) solid mixture at500x magnification n. **Source:** The authors.

Note that the material of the solid mixture (Figure 8) is formed by plates with some small fragments. In general, the plates are presented in a horizontal position, but the most prominent material presents these plates in a vertical position. When increasing the magnitude of the image, a uniform surface and some bubble-like elevations are observed.

Image of PEG 6000 with acetone and polysorbate (solid mixture) has a larger contact surface when compared to the pure PEG 6000 sample, even though the pure PEG 6000 shows slight porosity, it is not as noticeable as the sample that has the acetone and PEG 6000, the larger contact surface contributes to the retention mechanism (absorption and adsorption) of the hydrochlorothiazide drug and its subsequent encapsulation in the microcarrier.

Figure 9: Analysis of solid dispersion containing Hydrochlorothiazide at different image magnitudes.



(A) Solid dispersion with HCTZ at 100x magnification; (B) Solid dispersion with HCTZ at 250x magnification; (C) Solid dispersion with HCTZ at 500x magnification; (D) Solid dispersion with HCTZ at 1000x magnification; (E) Solid dispersion with HCTZ at 2000x magnification; (F) Solid dispersion with HCTZ at 5000x magnification. **Source:** The authors.

The SEMs of the solid dispersion with the drug (Figure 9) are quite similar to the white dispersion (Figure 7). But, note that the surface of this particle is formed by several overlapping fragments, similar to small scales. When a more isolated particle is observed, the difference in the surface is again perceived. In the latter case, the particle has small sheets superimposed on its surface, in addition to being more uniform. From the image it is possible to observe that in the solid dispersion containing the drug, the exterior is lighter than the center, in order to be able to formulate the hypothesis that the drug is in the interior part of the polymeric carrier, demonstrating the encapsulation of hydrochlorothiazide.

4.3 THERMOGRAVIMETRY AND DIFFERENTIAL SCANNING CALORIMETRY (DSC)

In the TG curve (green curve, A) of the drug, it is possible to observe an initial increase in the mass (which could be an analytical error or a characteristic behavior of the drug itself) that remains up to 55 minutes of analysis. After this period, the material undergoes decomposition in two stages: a larger stage that starts in 55 minutes and ends in 64 minutes; the last stage starts at 72 minutes and ends after 100 minutes. The beginning of the first

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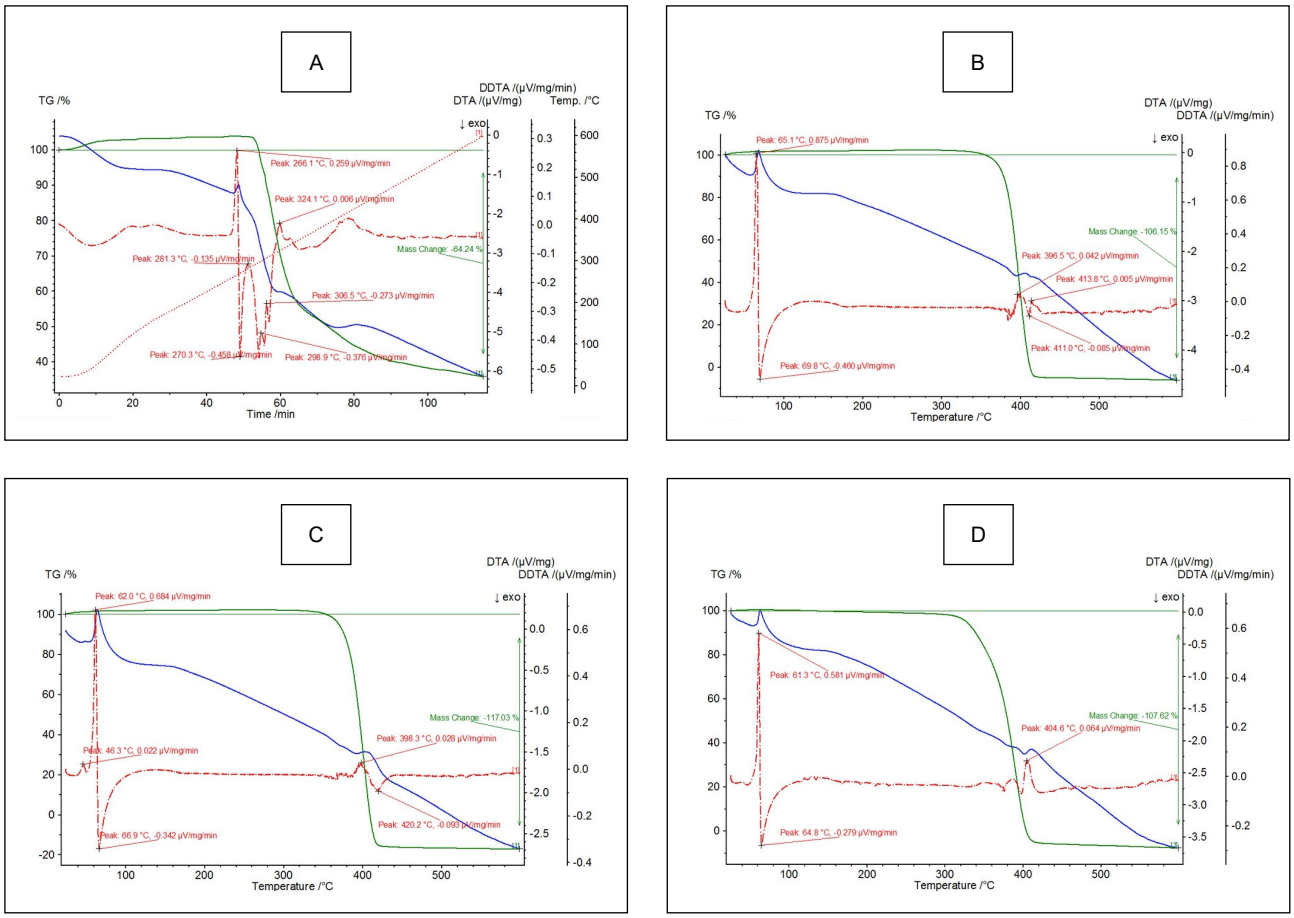
stage can be confirmed by the small endothermic peak present in the DTA curve (blue curve, figure 1), indicating the temperature that begins to fall (256.1 to 270.3ºC). The second is not so evident because it is less pronounced.

Figure 10: Thermogravimetry and Differential Scanning Calorimetry (DSC).



Caption: A) hydrochlorothiazide; B) PEG 6000; C) White Solid Dispersion; D) Solid dispersion containing hydrochlorothiazide. **Source:** The authors.

In the TG curve (green curve, b) PEG 6000, it is noted that it remains thermally stable until the temperature of 320ºC, where the material decomposes. The thermal decomposition of PEG 6000 occurs in a single step, ending at 420°C. The DTA curve (blue curve, figure b) shows only one endothermic peak, corresponding to the beginning of the analysis.

In the TG curves of the previous figure, we can have indications that the dispersion system containing the drug was formed, considering the similarity of the PEG 6000 curve of the dispersion. In mixtures, the TG curve has a similar profile. The material remains thermally stable up to 300°C and then undergoes decomposition in a single step that ends at around 400°C. The TG curves of the dispersions are very similar to the PEG 6000 curve, having a decomposition pattern in a single step.

In Table 4 it is possible to observe important details about volatility, melting point, degradation and mass loss.

5 FINAL CONSIDERATIONS

Drugs that have low solubility and permeability in physiological environments require treatments with the administration of high doses of drugs, which can cause side effects and non-adherence to therapy. Thus, it is essential to develop innovative solutions for the design and improvement of pharmaceutical forms and drug delivery systems. In this context, it is possible to correct the hydrophobic characteristics of the drug, improve its absorption and, consequently, reduce the dose administered from the application of solid dispersions.

The present research suggests the innovative application of the solid dispersion method employing a microcarrier consisting of polysorbate 80 and PEG 6000 suitable for improving the absorption of the drug hydrochlorothiazide. The analyzes showed favorable characteristics to the system developed according to the positive results, indicating a possible success of the applied method, suggesting an increase in absorption and, consequently, bioavailability, as well as an efficient drug delivery system.

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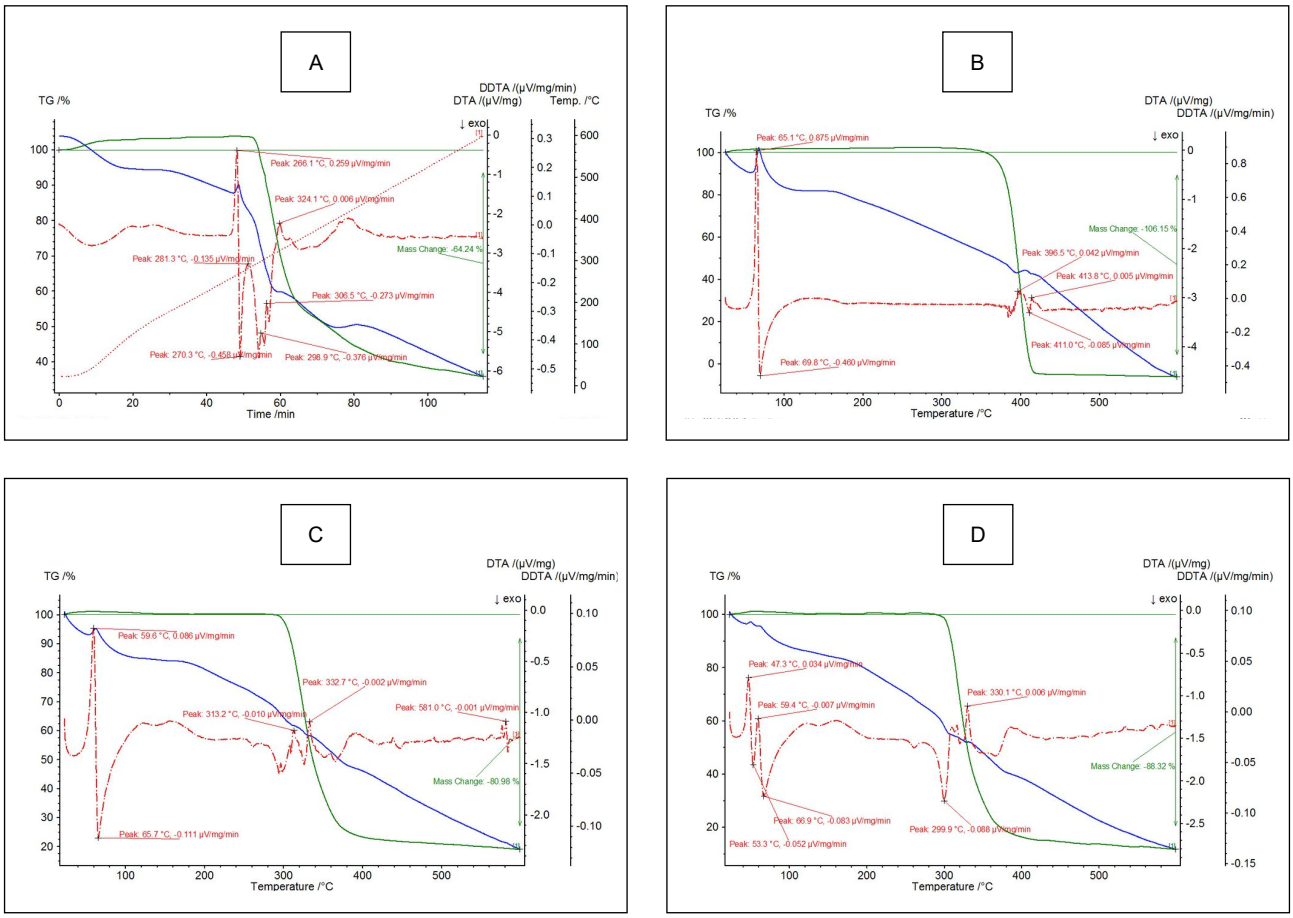
Figure 11: Thermogravimetry and Differential Scanning Calorimetry (DSC).



Caption: A) Drug; B) PEG 6000; C) physical mixture (1:1) Peg 6000+ hydrochlorothiazide; D) Physical mixture (1:1) of Peg 6000, polysorbate 80 and hydrochlorothiazide. **Source:** The authors.

Table 4: Thermal data of analyzed materials.

Materials	volatility	Melting Point	Degradation	Mass change
hydrochlorothiazide	266,1°C	270°C	324,1°C	64,24%
PEG 6000	65,1°C	69,8°C	413,8°C	106,15%
White Solid Dispersion	46,3°C	62,0°C	402,2°C	117,03%
Solid dispersion containing hydrochlorothiazide	61,3°C	64,8°C	404,6°C	107,62%
physical mixture (1:1) Peg 6000+ hydrochlorothiazide	59,6°C	65,7°C	581,0°C	80,98%
Physical mixture (1:1) of Peg 6000, polysorbate 80 and hydrochlorothiazide	47,3°C	53,3°C	330,1°C	88,32%

Source: The Authors.

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