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Determination of the Impact Caused by Direct Compression on the Crystalline State of Rupatadine Fumarate 10 mg Tablets

Luis Castillo Henríquez[1,2,*], Rolando Vargas Zúñiga[1,3], German Madrigal Redondo[1,3], Gustavo Carazo Berrocal[1,2], Georgia Hanley Vargas[1]

[1]Pharmacy Faculty, University of Costa Rica, Costa Rica, Postal Code 11501-2060, San José, Costa Rica
[2]Laboratory of Phytopharmacology and Pharmaceutical Technology (LAFITEC) of the Institute of Pharmaceutical Research (INIFAR), Costa Rica, Postal Code 11501-2060, San José, Costa Rica
[3]Laboratory of Biopharmacy and Pharmacokinetics (LABIOFAR) of the Institute of Pharmaceutical Research (INIFAR), Costa Rica, Postal Code 11501-2060, San José, Costa Rica

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***Corresponding author:** Luis Castillo Henríquez

Abstract **Original Research Article**

The aim of this study is to determine the impact caused by direct compression on the crystalline state of two prototypes of Rupatadine fumarate 10 mg tablets. The tablets were manufactured through direct compression. Five grams powdered tablets samples were taken randomly for analysis through DSC, TGA and XRD. The results were analyzed by making a comparison between their crystalline characterization and the one shown by the active pharmaceutical ingredient, excipients, the placebo and the powdered formula before compression. The active pharmaceutical ingredient showed a melting point at 201.38 °C, which decreased 2 – 3 °C in the tablets' thermograms. Placebos presented an endotherm at 228 °C characteristic of amorphous lactose's melting point. The only thermal change presented between the tablets and the other samples is the crystallization of amorphous lactose around 172 – 176 °C. X-ray diffractograms showed an increased intensity for the peaks of α - lactose monohydrate after compression and no changes regarding the active pharmaceutical ingredient. The comparison done between the analyses, confirmed that compression didn't impact the crystalline state of Rupatadine fumarate. However mechanical treatment and the influence of the excipients caused the fusion peak to shift towards lower temperatures. Lactose's crystal lattice suffered the greatest impact caused by compression, which generated the crystallization of the amorphous region present in that raw material. Nevertheless, such modification doesn't alter the prototypes' aptitude for being developed into a final solid pharmaceutical form and it is not a situation that affects the product's quality.

Keywords: Compression impact, Crystallization, Direct compression, Polymorphism, Rupatadine fumarate, Tablet.

INTRODUCTION

Tablets are the most common pharmaceutical form designed for treatment. Patients prefer taking tablets because they're easy to take and handle. Additionally, they're considered more suitable for large scale production and are more cost effective [1, 2].

Although direct compression is the most economical technique for tablet manufacturing, the method is affected by the attributes of raw materials. Some of their properties have been found to affect the parameters of the compressed solid product; like the crystallinity, moisture content, tensile strength, particle size, surface area and density. Therefore, excipients' properties and their impact on the performance of the solid formulation must be studied [3-5].

However, compression can induce physicochemical changes in bulk powders of the excipients and in the API as well. From the mentioned properties of raw materials, the most important one is the crystallinity, which is directly involved in the compactibility, tablet hardness, lamination, disintegration time and dissolution rate. The previous is really important because tablets should be able to withstand the rigors of the manufacturing processes and in the distribution system as well [1, 5].

Despite the reports on mechanical studies of tableting, there are few investigations describing the changes in physicochemical properties caused by the compression process. Specifically, those regarding the crystalline state of the API and the matrix of the formulation [5].

Several manufacture operations within the compression process, such as milling, mechanical dispersive techniques, high shear mixing and granulation; use mechanical energy for the physical manipulation of the formulation mixtures. This can destabilize crystalline and amorphous phases leading to phase transitions [5-7].

However, compression causes the greatest changes in terms of the crystal lattice. During the compression process, solid particles rearrange and the massive force is able to cause their deformation. This is similar to the formation of large crystals or aggregates when melting. Additionally, the compression reduces the distance between the molecules and their interparticulate porosity, causing particles to fragment and form a compact [6].

Precisely, the distance reduction between the molecules is an endothermic process that requires a considerable amount of energy in order to form a compact with a high surface area. On the other hand, particle bonding during compression is an exothermic process that can be explained through different mechanisms such as solid bridges, distance attraction forces and mechanical interlocking [1].

The components of the bed powder can suffer various physical transformations when subject to compression, such as Amorphous – Crystalline, Anhydrate – Hydrate and Polymorphic transitions. Amorphous and crystalline forms of the same molecule can show a different behavior during the manufacturing process. It is important to mention that many pharmaceutical excipients exist in an amorphous state, which seems to improve the handling and offers better mechanical properties, especially regarding aqueous solubility [5, 6, 8].

Polymorphism constitutes a factor that can't be ignored since the different arrangements in the crystal lattice of the raw materials, cause solids to have different physicochemical properties that can potentially influence the ones of the drug product and therefore, the therapeutic effect. Thus, regulatory entities like the FDA have highlighted their concern about the establishment and declaration of the API's and excipients' polymorphic transitions when filling dossiers [9-11].

But also, due to the mechanical stress induced by the compression process, nucleation sites can be formed leading to physical or chemical reactions, decreasing the physicochemical stability of the tablets. Even though only a small fraction of a formulation may undergo a physical change, it can represent a risk for the quality of the final product. The identification, monitorization and characterization of such transitions due to compression are commonly done through the combination of different analytical techniques such as DSC, TGA, XRD, NMR, and Raman Spectroscopy [7, 9, 12].

This investigation focuses on the determination of the impact caused by direct compression on the crystalline state of two prototypes of Rupatadine fumarate 10 mg tablets, by making a comparison between their crystalline characterization and the one shown by the API, excipients, the placebos and the powdered formulas before the compression.

The mentioned characterization and analysis were done through DSC, TGA and XRD.

MATERIALS AND METHODS

Materials

Table-1: Materials used for the research and formulation prototypes.

Raw materia	Manufacturer	Formula 1	Formula 2
Rupatadine Fumarate	Enaltec laboratories India, batch No. EL-03/L095/16025	✓	✓
Lactose monohydrate	DFE Pharma, batch No. 1010KX2	✓	✓
Microcrystalline cellulose	DFE Pharma, batch No. 100202	✓	✓
Sodium croscarmellose	JRS Pharma, batch No. 7111512407	✓	✓
Magnesium stearate	Helianthus, batch No. MGSV150475	✓	✓
PVP K-30	Ashland, batch No. 0001855552	X	✓

Methods

Manufacturing

The tablets were manufactured through direct compression using an Adept tablet press machine, model D – D – 27 with 1/8 inch punches. For each formulation prototype, the hardness of the tablets was maintained between 5 – 6.5 kp. The target weight per tablet was 120 mg ± 5 %.

Crystalline characterization

The analyses done to the tablets were compared to the ones performed previously to the placebos, the powdered formulas and the API. Five grams of powdered tablet samples of each formula were taken randomly and transferred to the test site under controlled conditions of temperature, light and humidity. The conditions and specifications of the equipment used were the following:

Differential Scanning Calorimetry

Equipment: DSC TA Instruments model Q200.

Conditions:

- Aluminum capsule.
- 100% Nitrogen Atmosphere 10 psi.
- Flow rate: 40 mL / minute.
- Heating series: isotherm at 20 °C for 5 minutes, then increase 10 °C / minute.
- Temperature range: 20 °C to 250 °C.
- Sensitivity Instrument and Recorder: Sensitivity 0.1 uW.
- Temperature precision: ± 0.05 °C.
- Temperature accuracy: ± 1 °C.
- Calorimetric precision: ± 0.1 %.
- Calorimetric reproducibility: ± 0.1 %.
- Weight: 4 to 5 mg sample.
- Calibration with Indium and distilled water.
- Three replicas.

Thermogravimetric Analysis

Equipment: TGA TA Instruments model Q500.

Conditions:

- 100% Nitrogen 10 psi Atmosphere.
- Volume flow: 40 mL / minute.
- Heating rate: 10 °C / minute.
- Temperature range: 20 °C to 1000 °C.
- Weight: 4 to 5 mg sample.
- Sensitivity: 0.1 ug.
- Isothermal temperatura accuracy: ± 0.1 %.
- Isothermal temperatura precision ± 0.1 %.
- Three replicas.

X-ray Diffraction

Equipment: Diffractometer: PANalytical Empyrean.

Conditions:

- Temperature: Room temperatura 25 °C.
- Nickel filter.
- Copper anode source Kα [λ 1, 54 A°].
- Polymethacrylate sample holder.
- Continuous analysis at 0.1° per second in the range of 3° to 40 ° 2θ.
- Gas detector with photodiodes.
- Weight: 10 to 15 mg sample.
- Three replicas.

RESULTS

Differential Scanning Calorimetry

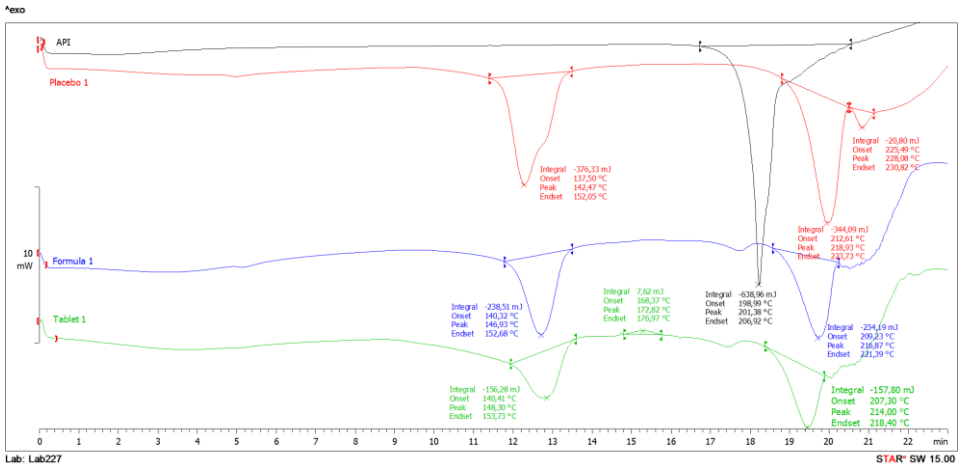

Fig-1: DSC analysis of prototype's 1 samples

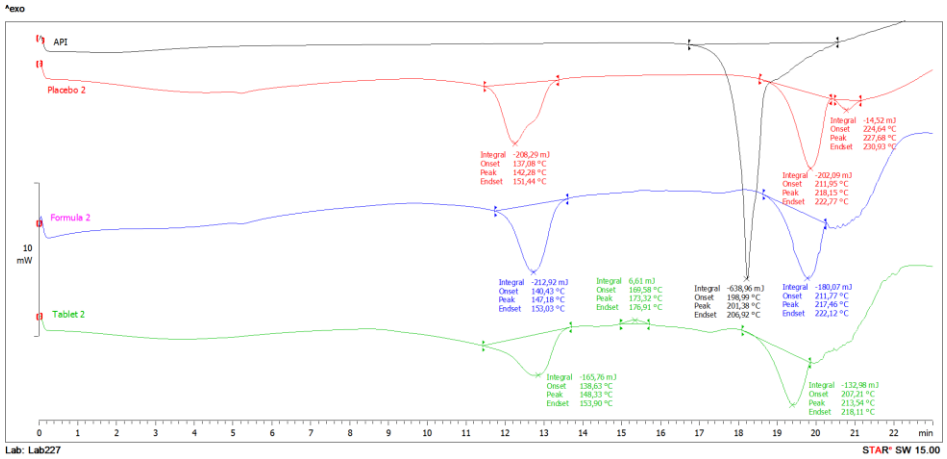

Fig-2: DSC analysis of prototype's 2 samples

Figures 1 and 2 illustrate a thermal event for the API at 201.38 °C. In the two prototypes it is possible to observe that the placebo, powdered formula and tablet show two characteristic endothermic events; one around 142 – 148 °C and the other one near 214 – 218 °C.

Moreover, it can be seen that only the placebos show an endothermic event around 228 °C, which is characteristic of an amorphous material. However, the only thermal change presented between the tablets and the other samples, is an exothermic peak that appears around 172 – 176 °C.

Thermogravimetric Analysis

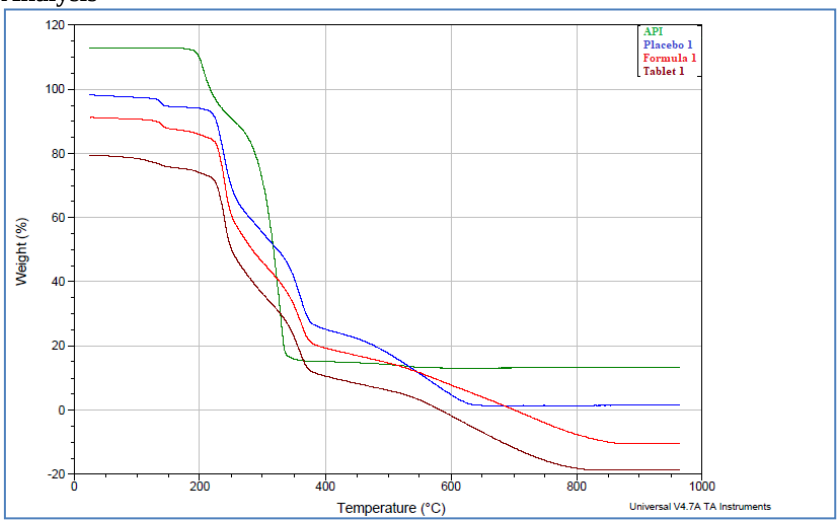

Fig-3: TGA of prototype's 1 samples

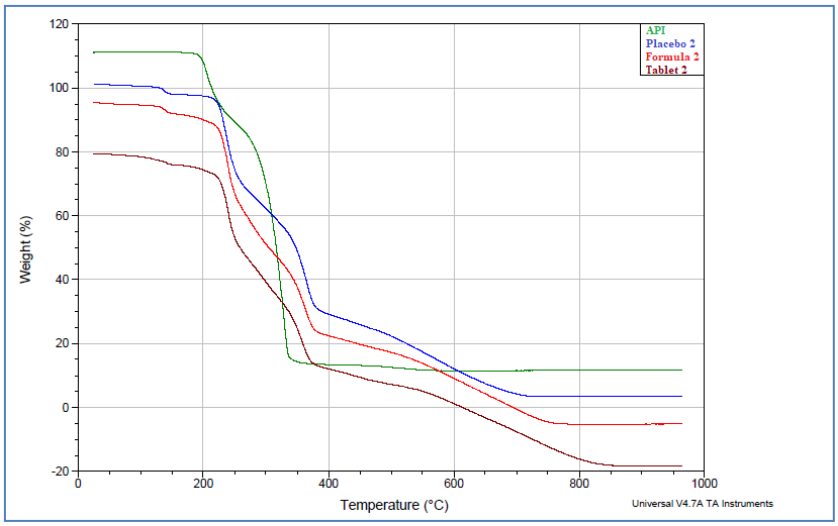

Fig-4: TGA of prototype's 2 samples

Figures 3 and 4 show no mass decrease from 0 – 150 °C for the API. However, there's evidence of a 20 % of mass loss between 205 – 208 °C. The three samples; placebo, powdered formula and tablets of the two prototypes, exhibit a very similar behavior for this analysis. Their thermograms show an initial mass reduction between 140 - 210 °C. A second mass loss is presented from 210 - 280 °C.

X-Ray Diffraction

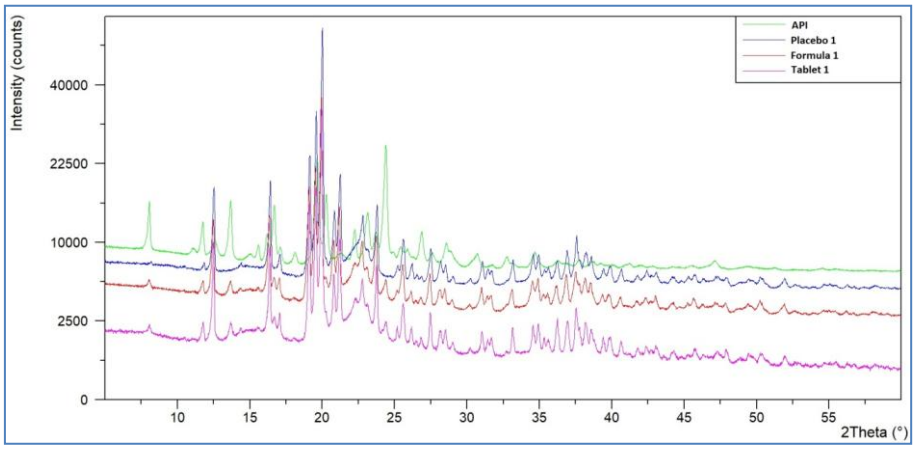

Fig-5: XRD analysis of prototype's 1 samples

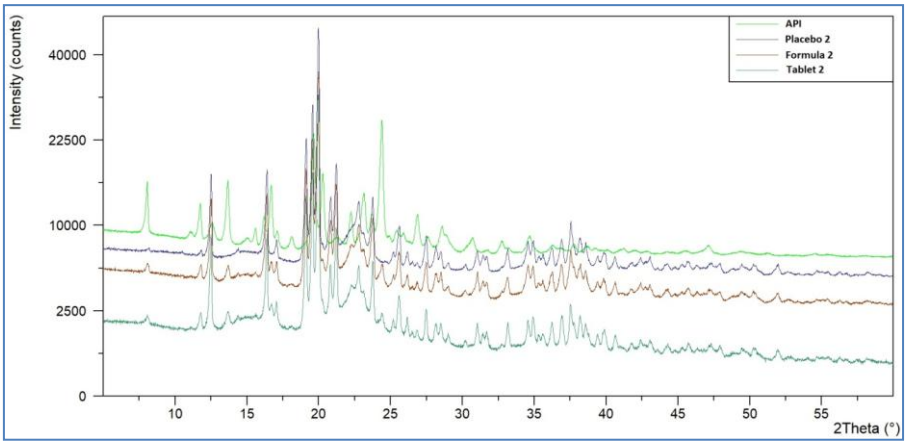

Fig-6: XRD analysis of prototype's 2 samples

Figures 5 and 6 exhibit a classic crystalline pattern. Before compression, the powdered formulas show the API's six characteristic peaks, which can be identified in the two prototypes tablets as well. The mentioned peaks are: 13.6, 17.0, 20.2, 21.3, 23.6 and 25.8 2θ [13,14].

The placebo and powdered formulas show other main peaks that are not related to the API at 12.4, 16.4, 19.8, 20.7 and 22.7 2θ. Similar diffraction patterns were observed for the tablet formulations. However, the diffractograms of each tablet prototype differ from their corresponding placebo and powdered formula in the intensity of the peaks at 12.4, 16.4 and 19.8 2θ.

DISCUSSION

Additional to the execution of compatibility studies, it is also important to analyze the impact generated by the manufacturing processes on the properties of raw materials and the finished product [15].

In a previous investigation, we characterized the thermal behavior of the API, placebos and the powdered formula, where we were able to conclude that no interaction or incompatibility between the raw materials was presented. Briefly, the thermal event presented by the API at 201.83 °C in the DSC analysis is its melting point, followed by its decomposition as confirmed by the mass loss in the TGA thermogram [15].

The endothermic event showed by all samples around 142 – 148 °C in the DSC analysis, including tablets, is due to the dehydration of lactose monohydrate, which matches their first mass loss presented in the TGA thermograms [15-19].

Also, earlier work from our laboratory has demonstrated the existence of only one crystalline form for Rupatadine fumarate, which is form A. Thus, a polymorphic transition is not contemplated as a possible effect on the crystalline state of the API due to compression. The diffractograms for the placebos, powdered formulas and tablets in figures 5 and 6 show that the characteristic peaks of the API are still present but are less intense because its presence in the formulations is reduced compared to its individual analysis [13].

Although it seems that Rupatadine fumarate didn't change its solid state nature at all, it is possible to notice that its melting point decreased 2 – 3 °C in the

tablets samples. This is because the excipients can lower this physicochemical property of pure drugs during compression, by causing a surface fusion before its normal melting [1,2].

However, figures 1 and 2 present an exothermic event for the tablets which is related to compression, at 172 – 176 °C. Nevertheless, the new peak doesn't match to a mass loss in the TGA presented in figures 3 and 4, so a chemical reaction such as decomposition is discarded. In DSC analysis, an exothermic peak can also be explained by a change in the crystalline structure of the sample [15].

Taking into consideration that the API didn't suffer any physical or chemical change and a new exothermic peak appeared in the tablets' DSC analysis, it is important to analyze which raw materials could have suffered a change in their crystal structure, specially the diluents because they are present in a greater proportion.

Regarding microcrystalline cellulose, we chose polymorph I which is widely used as a pharmaceutical aid for compression because of its adequate compactability and compressibility properties. The revised literature states that neither polymorphic form I nor II are affected by compression. Therefore, a change in the crystal lattice of this excipient is discarded as well [4, 20].

On the other hand, lactose monohydrate's thermal behavior has some particular aspects that are worth analyzing. This is because there are three other polymorphic forms involved: Stable anhydrous α - lactose, unstable anhydrous α - lactose and anhydrous β - lactose. In addition, amorphous lactose can also be presented [8, 17, 21].

α - lactose monohydrate has been reported as the most common present form in commercial batches. A study conducted on several samples revealed that at temperatures close to 177 ° C an endothermic event may occur due to the anomerization of α - lactose to β - lactose. In addition, it is mentioned that a small amount of water vapor is enough to cause such a physical change at temperatures higher than 150 °C, which is totally valid since it is difficult to think that all water within the crystal lattice has been removed in its first endotherm, taking into account that lactose has three [17].

However, the mentioned event was not possible to confirm in our study since the thermograms didn't show an endothermic peak at that temperature. Also, the melting point of β - lactose, which should be present at 234 °C, was not possible to appreciate either [17,22].

Nevertheless, the anomerization in the tablets can be overlapped with the crystallization exothermic event of the amorphous phase that is reported to occur at 172 °C. A way of confirming the crystallization is through the analysis of the respective TGA thermograms, which in our case didn't show a mass loss, as should be expected since this is conceived as a physical change. Precisely, the third endotherm for lactose in the DSC analysis of placebos, powdered formulas and tablets, around 214 – 218 °C corresponds mostly to the melting of the stable α - lactose crystals which is reported to happen at 217 °C and it is followed by its decomposition [17].

The extra endotherm presented by the placebos helped to confirm the crystallization that the amorphous phase suffered due to compression, since the melting point of amorphous lactose is established to occur close to 223 °C and it is not presented in the tablets DSC thermograms [17].

X-ray diffraction is a very relevant technique that can be used to confirm the previously discussed results. Figures 5 and 6 show the classic peaks of α - lactose monohydrate in the placebos and the powdered formulas, specially its main peaks at 12.4, 16.4 and 19.8 2θ. In the mentioned samples, it is quite difficult to identify the main peaks of β - lactose at 10.5 and 20.9 2θ. This is probably due to an overlap with the crystalline signals of the other raw materials and to β – lactose's relatively low presence [21].

Even though the product of the crystallization is the stable form of α - lactose, the presence of water in the powdered samples led to its transformation into α - lactose monohydrate. Since the X-ray diffraction technique doesn't eliminate water from the crystal lattice as DSC does, in the analysis of the tablets it is possible to observe α - lactose monohydrate's peaks a bit more intense as a consequence of the crystallization of amorphous lactose induced by compression [22].

Although amorphous lactose has been found to be more compressible than the crystalline forms, the change induced by compression doesn't represent a disadvantage for the present formulations, since α - lactose monohydrate is still considered one of the most useful diluents because of its good flowability and consolidation by fragmentation. Also, it is important to remember that the selected batch for the development was mostly constituted by this crystalline form [8].

CONCLUSIONS

Special attention should be paid for the evaluation of the manufacturing processes, specifically regarding the influence on the material attributes. The crystalline state of the raw materials for the development of pharmaceutical products is of great interest. Different crystalline forms can provide advantages in terms of formulation and the performance

of the pharmaceutical form, while other crystal arrangements may lead to poor dissolution, low bioavalability and therefore, a reduced therapeutic effect.

The comparison between the analyses of the tablets and their corresponding placebos and powdered formulas that has been done in this investigation, confirmed that compression didn't impact the crystalline state of the API, Rupatadine fumarate, since there's only one possible crystal arrangement. However, the API's fusion peak shifted towards lower temperatures clearly by the mechanical treatments and by the influence of the excipients.

However, the analyses of the tablets suggest that lactose's crystal lattice suffered the greatest impact caused by compression. The implemented manufacturing process generated the crystallization of the amorphous region present in that raw material, which was only possible to realize by the interpretation of the DSC thermograms, where an exothermic peak appeared around 172 – 176 °C without causing mass loss in the TGA. This was complemented by the increase in α - lactose monohydrate's peak intensity, presented in the XRD diffractograms of the tablets.

Although compression did influence the crystal lattice of one of the components of the matrix, such modification doesn't alter the aptitude of the prototypes for being developed into a final solid pharmaceutical form, because it is not a modification that puts at risk the product's quality.

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Disclosure statement

The authors report no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient, **DSC:** Differential Scanning Calorimetry, **FDA:** Food and Drug Administration, **NIR:** Near Infrared Spectroscopy, **NMR:** Nuclear Magnetic Resonance, **TGA**: Thermogravimetric Analysis, **XRD**; X-Ray Diffraction.

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