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Research Article

Identification of Solid Phase State of Hemi-Dihydrate atorvastatin in Pharmaceutical Raw Materials

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Abstract: Determining the spatial configuration of the structures of compounds used in the production of medicines is extremely important due to the different characteristics of each of them in its solid state and therefore its different qualities of each for use as pharmaceutical raw material. This study aimed to identify the phase of the solid state of Atorvastatin hemi-dihydrate, a lipid-lowering medication HMG-CoA reductase widely use in the present and their characterization by four different instrumental analytical techniques: X-ray diffractometry, differential scanning calorimetry, thermogravimetry and infrared spectroscopy, comparing the obtained analytical results with those found in the literature. Using data obtained from these four techniques are able to show that the study sample exists predominantly in the 27 form of amorphic hemi-dihydrate calcic atorvastatin.
Keywords: Atorvastatin, Drugs, Pharmaceuthicals, Polimorphism, Solid Estate.

INTRODUCTION

Polymorphism is defined as the ability of a substance to exist in various crystalline forms with a different spatial arrangement of the molecules in the crystal, these compositions have different spatial forms with different physicochemical characteristics in the solid state and different dissolution and absorption behaviors. Another possibility is the existence of an amorphous state, which is characterized by a disordered conformation of the molecules, these compounds have advantages and disadvantages with respects to the polymorphic states, as it favored the dissolution process also an amorphic state are typically unstable, have an increased hygroscopicity and tend to crystallize[1, 2].

Some of the pharmaceutical characteristics that can be affected are the melting point, hygroscopicity, physicochemical stability, apparent solubility and dissolution and hence its bioavailability. It is possible that the conformation of these compounds varies from one to another crystalline or amorphous state as result of normal processes in the manufacture and distribution of drugs such as mixing, micronization, wet granulation, transport and light compression, among others. Because of all these, is very important to be clear which polymorph or amorphous structure is available at the time of manufacture solid dosage forms and that because the effect of the manufacturing process there's nochange in the solid state[2, 3].

The aim of this work is to determine the possible existence of polymorphic forms, amorphous or even pseupolimorphism in raw material used in the production of medicines and to characterize it by the complementary use of four instrumental techniques: X-ray diffraction, calorimetry differential scanning calorimetry, thermogravimetry and infrared spectroscopy and compare it with other studies found in the literature. Atorvastatin was used as the test substance which was provided by the Costa Rican pharmaceutical industries who use it, due to some specific situation of the product in manufacture it or a in the quality control . Atorvastatin is a lipid-lowering medication Patent 1991. The molecular formula is C33H34FN2O5, chemical name [R- (R *, R *)] - 2- (4-fluorophenyl) beta, delta-dihydroxy-5- (1- methylethyl) -3-phenyl-4 - [(phenyl-amino) carbonyl] -1-pyrrole-1heptanoico calcium salt and the Anatomical-Therapeutic-Chemical (ATC) Classification of the World Health Organization identifies with the code:

C10AA05. The drug is a competitive inhibitor of hydroxymethylglutaryl CoA reductase enzyme, responsible for the conversion of 3.hidroxi-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol [4, 5, 6].

The HMG-CoA reductase inhibitors are indicated as an adjunct to diet in the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) in mixed hyperlipidemia, hypercholesterolemia combined with hypertriglyceridemia among other diseases with high levels of LDL and total cholesterol. Atorvastatin is rapidly absorbed after oral administration and the maximum concentrations present in 1 to 2 hours post administration. It has an absolute bioavailability of 14%. Has first pass metabolism in the gastric mucosa, the volume of distribution is 380 L and joined by about 98% to plasma proteins[4,7,8].

MATERIALS AND METHODS

A qualitative study on a sample of atorvastatin was conducted by comparing physicochemical parameters reported by the scientific and / or patent literature, and those found in the experimentally in the laboratory.

Samples of raw material provided by a national pharmaceutical industry, which were taken at random and taken to the test site under controlled conditions of light, temperature and humidity were used.

The results obtained in each of the studies are compared with the state of art found in the revised bibliography to be able to find similarities and to conclude on the crystalline or amorphous state of the sample.

There is no official Pharmacopoeia standard for comparison so the identification test must be conducted using its physicochemical properties by the techniques described in the United States of America Pharmacopeia 33 and other lscientific literature for example Profiles Drugs Substances, and Patents [9,10,11,12].

Tests, equipment and the same conditions used for the characterization of atorvastatin are detailed below:

X-ray diffractometry:
Equipment: Diffractometer: Brand Bruker D8 model. Conditions: 25 ° C ambient temperature, filter Nickel, copper anode source Ka (l 1.54 A °) sample holder polymers, continuous analysis to 0.2 ° per second in a range of 3 ° to 40 ° 2θ , gas detector photodiodes, weight: 8-10 mg sample. Three replicas.

Differential Scanning Calorimetry
Equipment: brand DSC Q200 TA Instruments model. Conditions: Capsule aluminum, 100% nitrogen atmosphere 10 psi, flow rate: 40 mL / minute series of 10 ° C / min, temperature range 25 ° C to 250 ° C, and recorder instrument sensitivity: sensitivity 0 1 uW, temperature accuracy: ± 0.05 ° C, temperature accuracy of ± 0.1 ° C, calorimetric accuracy ± 0.1%, ± 0.1% calorimetric reproducibility, weight: 3-4 mg sample. Three replicas

Thermogravimetry
Equipment: TGA Q500 brand TA Instruments model. Conditions: 100% nitrogen atmosphere 10 psi, flow volume 40 mL / min, heating rate: 10 ° C / minute scan 0 ° C to 1000 ° C, weight 8-10 mg sample, sensitivity 0.1 ug , isothermal temperature accuracy of ± 0.1%, accuracy ± 0.1% isothermal temperature, mass accuracy ± 0.01%. Three replicas

Infrared Spectroscopy
Equipment: FTIR Brand Thermo Scientific Nicolet model 6700
Conditions: Tablet barium bromide, range 600 to 4000 cm^{-1}, temperature 25 ° C, relative humidity 30%

RESULTS AND DISCUSSION

X-ray diffractometry

The comparison of the XRD pattern shows the absence of a crystalline state in the sample analyzed due to the absence of characteristic peak. A classical diffractogram of a an amorphous structure shows no clear peaks with no definite pattern, however, there are two areas with a width characterizing bulge 2θ between 15 and 25 and between 5 and 10 2θ corresponding to the amorphous form 27 found in literature. The form 23, which is also shown in Figure 1, shows a higher packing, which is shown with a narrower bulge mainly in the second one at 15 to 20 2θ [10,13].

Figure 2 shows the diffractogram of the crystalline form 1 marketed by Pfizer which is totally different from the analyzed sample and confirm that the raw material is in an amorphous form [13,14].

The enclosed area in the circle shows the typical diffractogram for an amorphous state, where there´s no defined peaks, as can be observed in other crystalline forms. See Figure 2.

A differential comparison of diffractograms found in literature is performed, founding that the sample and the artof the amorphous structure forms 27 are the ones that show greater similarity. These diffractograms are not included but can be reviewed in the cited literature[10].

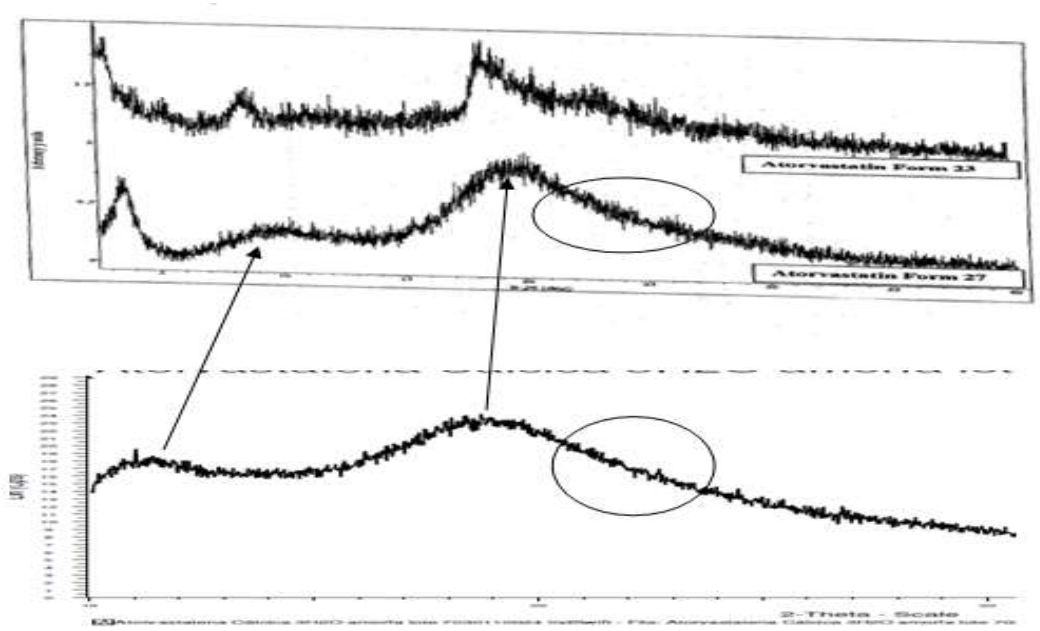

Fig-1: Comparison of the results shows diffractogram art amorphous forms for Atorvastatin 23 and 27 shown in the reference [10].

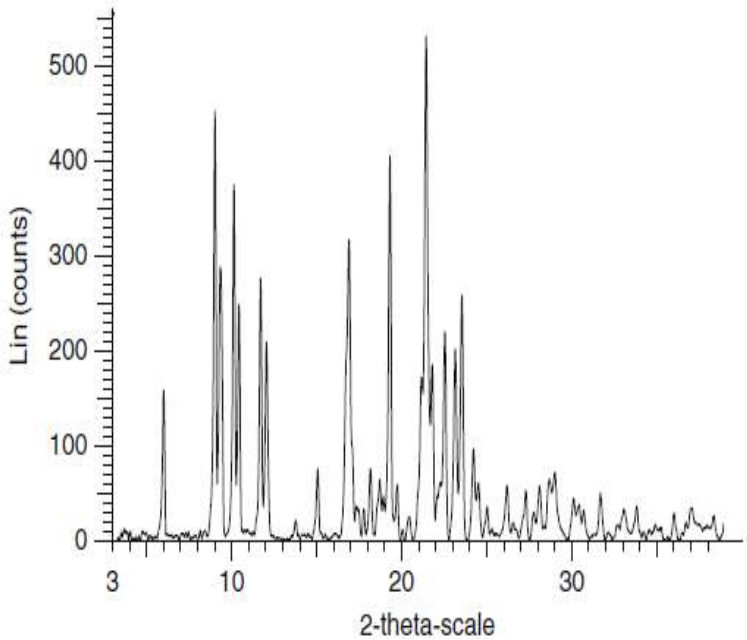

Fig-2: Polymorphic Form 1 Diffractogram Art marketed by Pfizer Lipitor [10,14].

Differential Scanning Calorimetry

Curves a, b, c, d and f, the upper figure shows the thermograms of the various samples of the 27 form atorvastatin. Curve e shoes the termograma of form 23. The assay sample shows mainly two endotherms; the first corresponds to a broad endotherm between 50 and 100 ° C which coincides with the art, and represents the dehydration of the three springs, as shown in TGA testing and the second endotherm represents the glass transition temperature Tg in an area ranging from 140 to 160 °C, with an approximate Tg of 154.6 ± 3.0 °C. These data alone cannot distinguish between the forms 23 and 27 as shown in the art, however, using with information obtained from the X-ray diffraction, it can be said that 27 form predominates. Is important to note that although the aim of this study is to quantify the total concentration of each of the amorphous forms present in the sample, it can be said that the sample has no contamination of crystalline form, but there may be some percentage of the amorphous form 23 in combination with the form 27, as there is similar pattern between the sample thermogram and curve e corresponding to form 23, where endotherms are more defined due to the higher packing compared to the 27 form. The sample decomposition begins at 200 ° C as shown in the TGA and DSC thermogram [10,13].

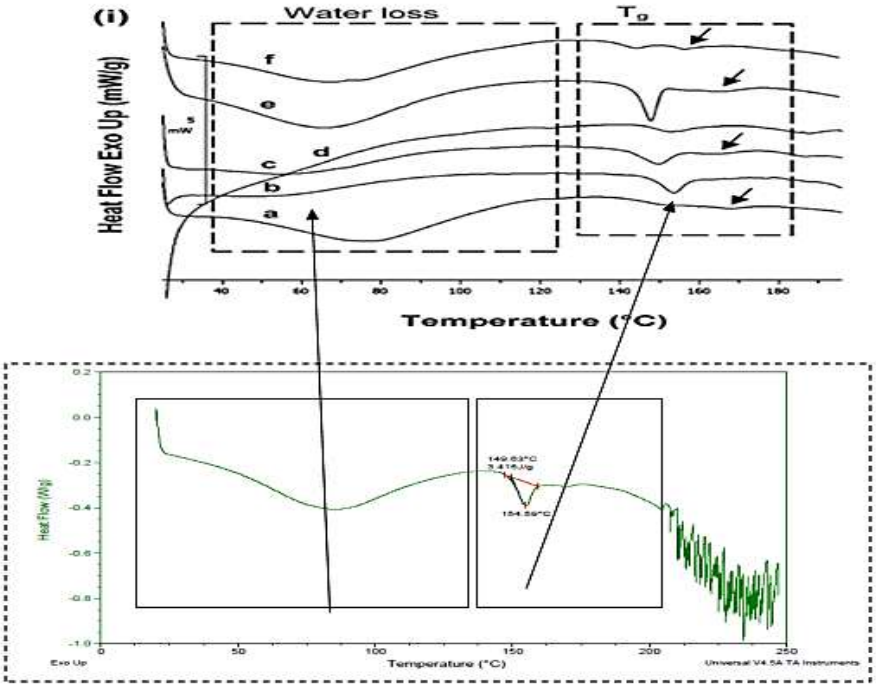

Fig-3: Comparison of results of DSC of the sample and the art [13].

Thermogravimetry

According to structural formula, the water of hydration is approximately 4.5% of the total sample weight. As seen in art as in the test, the mass loss between 40 ° C and 100 °C represents 4.5% of loss, corresponding to the three waters of hydration of the sample. Also the decomposition of the sample is shown from 200 ° C, which coincides with the thermogram of Figure 4 (this is shown by the enormous loss of weight, about 84.5% in the thermogravitogram). It cannot be differentiated with this technique between forms 23 and 27, however the sum of the assays referred above will demonstrate that the predominant form is the form 27 [10,11,12,13].

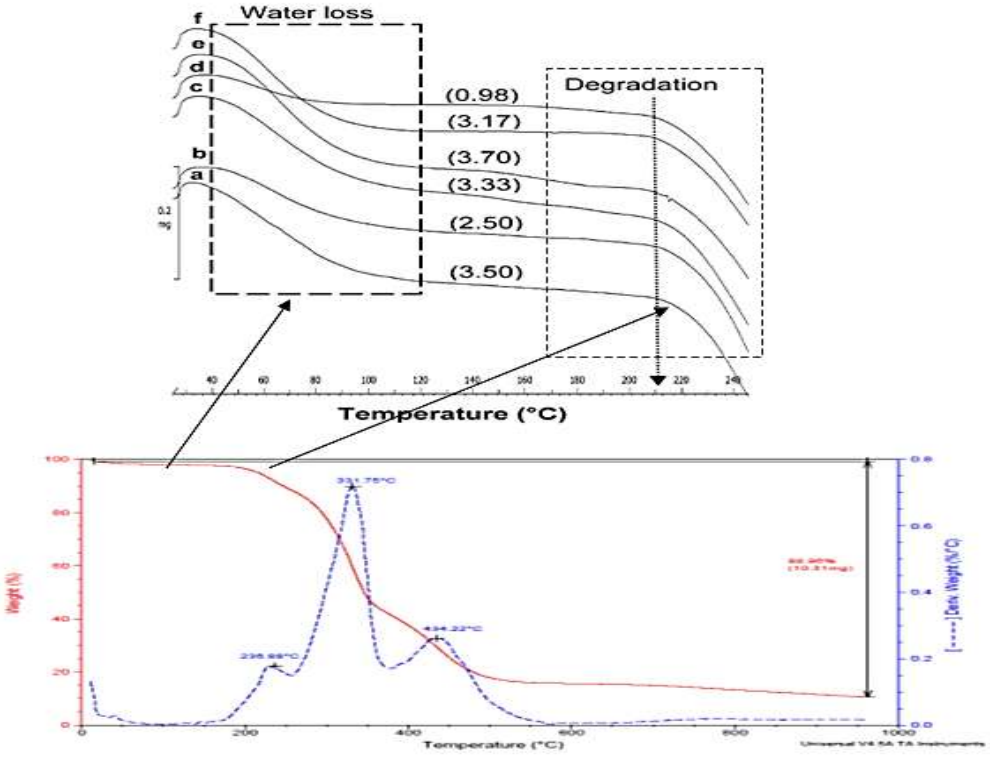

Fig-4: Comparison of results of TGA of the sample with art [13].

Infrared Spectroscopy

The characteristic peaks of Atorvastatin can be observed in the infrared spectral fingerprint of the sample. The similarity of these bands (enclosed in circle) is evident. For example the main FTIR peaks are due to 1651cm $^{-1}$ bands corresponding to C = O carbonyl group of the amide, the band 2903 cm $^{-1}$ corresponds to the aromatic CH group, the band 1595 cm $^{-1}$ corresponds to aromatic C = OC, bands 3365 cm $^{-1}$ correspond to OH and the band 3228 cm^{-1} corresponds to the NH group. It is also found that the characteristic band at 800 cm $^{-1}$ is specific for crystalline Form 1 of atorvastatin and this does not appear in the infrared spectrum of the sample indicated by the bold arrows in Figure 5. This band is observed in the infrared spectra of crystalline form 1. (See figure 6) [10].

The absence of the peak at 800 cm $^{-1}$ characteristic of the crystalline form 1 of calcium atorvastatin demonstrates the absence of this crystalline form in the sample, theory that is which is confirmed by previous trials.

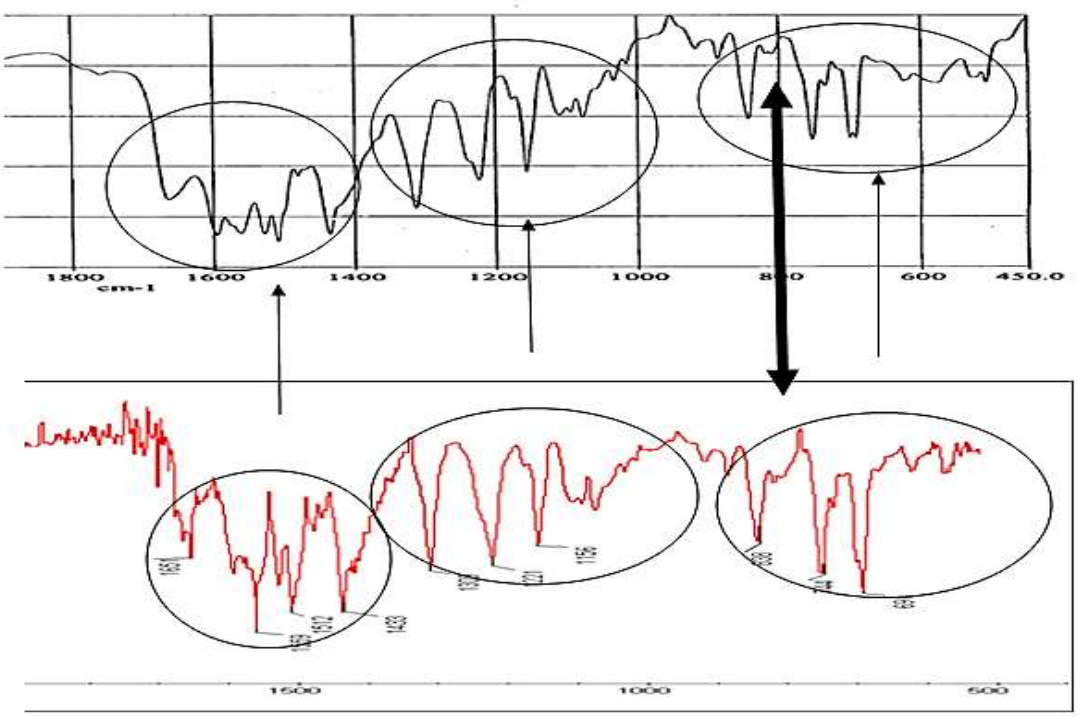

Fig-5: Comparison of infrared spectrum of the sample with the art [10].

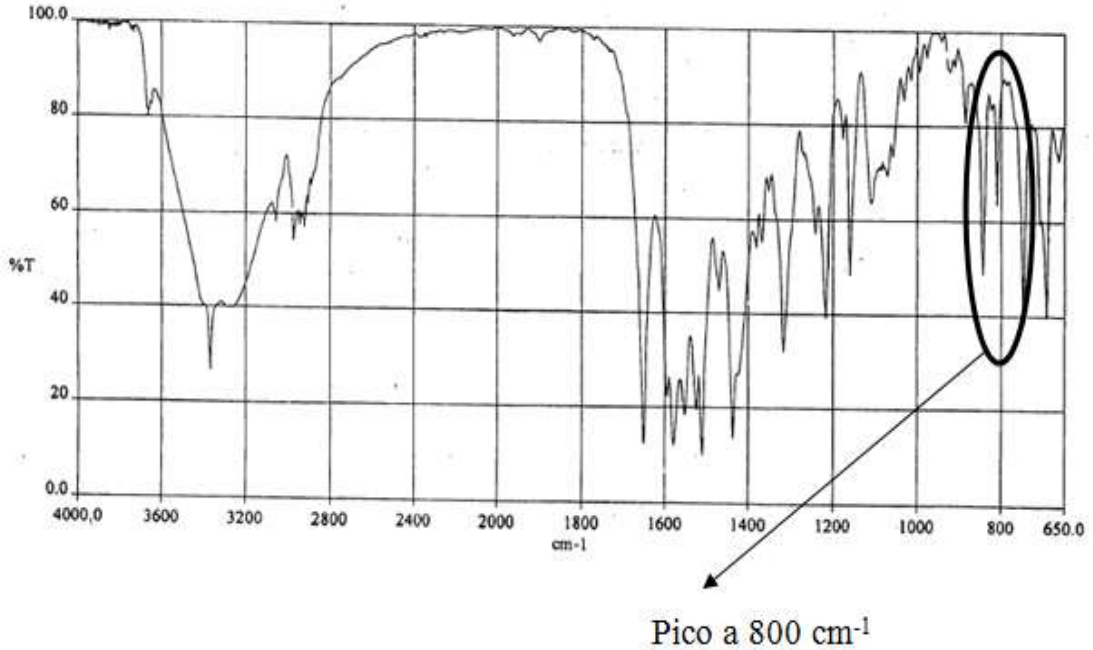

Fig-6: Infrared spectrum of crystalline form 1 of calcium atorvastatin [10].

CONCLUSIONS

With this information it can be concluded that: The characterization by X-ray diffraction shows the existence of the amorphous form 27 of hemi-calcic atorvastatin 3H2O. The characterization by X-ray diffraction proves that there is nocrystalline polymorphic forms contain in the sample.

Assay Differential scanning calorimetry shows the existence of two endotherms one between 40 ° C and 100 ° C which represents the loss of water, and the other between 140 ° C to 160 ° C which corresponds to the Tg. Due to the narrowness of the Tg endotherm of the sample, there may be a small proportion of the sample in form 23, however form 27 is predominant.

Thermogravimetric assay demonstrates the loss of mass by 4.5% between 40 ° C and 100 ° C, corresponding to the three waters of hydration presents the sample. There is a further mass loss after 200 ° C corresponds to decomposition of the sample.

Characteristic bands in the infrared showed the presence of amorphous atorvastatin form 27. The absence of the characteristic peak at 800 cm $^{-1}$, demonstrate the absence of crystalline forms in the sample.

In general we can conclude that the trials demonstrate the predominant existence of amorphous 27 form of hemi-calcicatorvastatina $3H_2O$, and total absence of crystalline forms in the sample.

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