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Journal of Chemical and Pharmaceutical Research, 2015, 7(5):76-80

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Solid state characterization of atorvastatin in drug products

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ABSTRACT

Two Atorvastatin marketed products with different composition and showing significant discrepancy in dissolution kinetics were subjected to solid state characterization. PXRD, DSC and FTIR didn't show any remarkable differences in the API of the tablet. However, the 19F ssNMR showed a mixture of atorvastatin forms for the product indicating a lower dissolution.

Key words: Atorvastatine, Tablet, SS-NMR, Dissolution Rate.

INTRODUCTION

Compared to other forms, solid oral dosage offers convenience, physical and chemical stability, ease of product handling, a high throughput and low manufacturing costs. However solid state properties have a profound impact on the solubility and stability [1, 2], thus raising some fundamental problems such as phase transformation control and prediction during the development process and manufacture [3].These push pharmaceutical companies to conduct systematic analyses of raw materials, semi -finished products and commercial formulations, using structural, thermal and spectroscopic analytical tools such as X-ray diffraction, scanning calorimetry and FTIR analysis [4, 5]. However, these analyses could fail to differentiate subtle details of the structures which require the use of very local techniques such as MAS-NMR [6-8]. The latter is a complementary technique to crystallography for obtaining structural information about solids, since the number of resonances in the spectrum is equal to the number of non-equivalent nuclei in the asymmetric structural unit. The method is particularly useful in cases where crystallographic examination is not possible because the sample is not crystalline or forms a complex compound. In comparison to PXRD analysis, MAS-NMR avoids the difficulties of growing good crystallinity as well as the detection of small quantities. NMR provides an immediate indication of the presence of any conformational multiplicity that may exist in the solid state; this technique is therefore especially suitable for the characterization of pharmaceutical polymorphs and enantiomers [9-14]. Given that 19F is a highly receptive nucleus, its NMR signals can reflect even slight changes in molecular arrangements. Moreover, 19F NMR could be an efficient tool to characterize drugs directly in their final dosage forms avoiding interference from excipients which are usually exempt of fluorine [14]. It has become evident that fluorinated compounds have a remarkable selling record in medicinal chemistry and play an important role in providing lead compounds for therapeutic applications [15-16].

The dependence of the kinetics of dissolution on the solid state is more pronounced for poorly soluble substances which are generally forced to intensive mechanical and physical transformations [17-18]; thus, control of its physical and chemical characteristics is becoming increasingly essential.

The aim of this study was to perform the solid state characterization of commercial drug samples available in the Tunisian market by comparing active pharmaceutical ingredients in low-dose tablets of Atorvastatin- a typical poorly water-soluble drug and representative of fluorinated pharmaceutical substances. At least 60 polymorphic

forms/solvates/hydrates of Atorvastatin have been patented and/or published [19]. Surprisingly, none with single crystal structure information has been reported on CSD (Cambridge Structural Database, 2013). However Wang *et al*. provided complete 13C, 19F and 15N isotropic chemical shift assignments for ATC-I that demonstrate the existence of two molecules in the asymmetric unit [20].

The utility of 19 F NMR in characterizing the active pharmaceutical ingredient in low-dose tablets was highlighted. This work was carried out as part of an effort to strengthen the credibility of national products and to improve monitoring and prevention capabilities in the generic industry.

EXPERIMENTAL SECTION

Pure substance of atorvastatin was obtained from Drugs Quality Control Laboratory of Tunis as pure compound readily available to be used for medical purpose. Commercial products (tablets) were purchased in a local drugstore. The Differential Scanning Calorimetric curves were obtained in a DSC-131 cell (SETARAM) using aluminum crucibles with about 4 mg of samples, under dynamic nitrogen atmosphere. The temperature range was from 30°C to 300°C at heating rate of 10°C min^{-1}.

The X-ray diffractograms of the powders were recorded between 5° and 35° (2θ), at room temperature, using a PANalytical X'Pert PRO with a copper anticathode.

Solid state magic angle spinning MAS-NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer. Samples were prepared in 4mm zirconium rotors. Measurement conditions were as follows: 90◦ proton rf pulse, 5 s; MAS frequency, 12 kHz; spectral width, 400 kHz ; and acquisition time, 2.6 ms; d1, 10s; p1, 2µs; NS, 600. The chemical shifts were referenced to the hexafluorobenzene C_6F_6. FTIR analysis was performed by BRUKER instrument (VERTEX 70) using an ATR with monoreflexion.

RESULTS AND DISCUSSION

A comparative study was conducted on two samples, ATR1 and ATR2, representing two low dose tablets of atoravastatin (Fig.1) and containing respectively lactose and calcium carbonate as the major excipient.

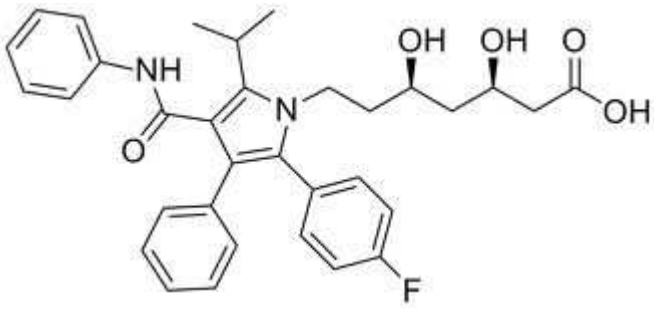

Fig.1: Chemical structure of Atorvastatine

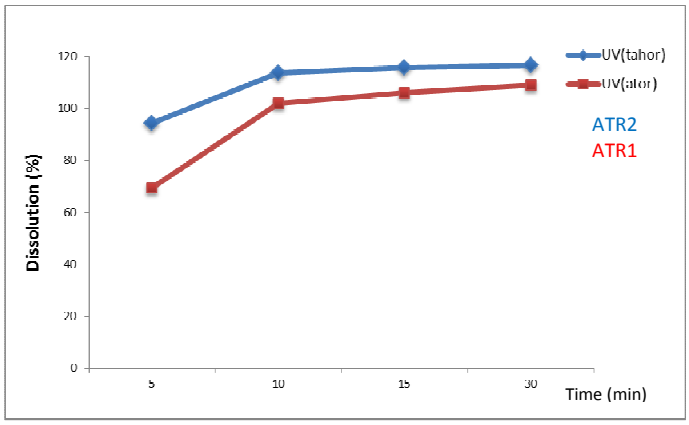

Fig.2 : Dissolution curves of tablets ATR1 and ATR 2

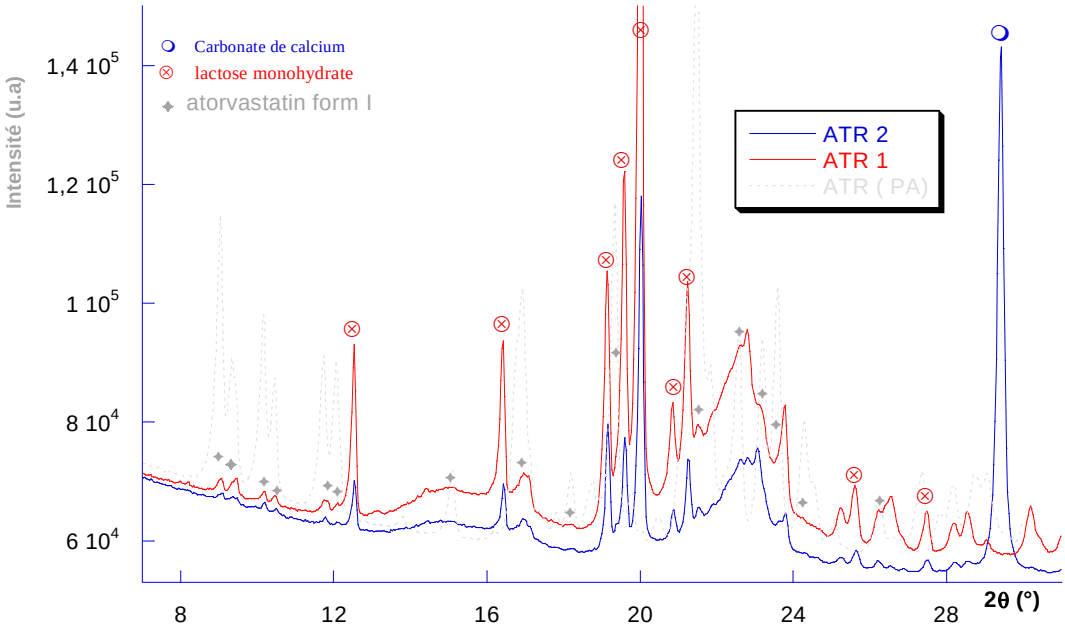

Fig.3 : X-ray patterns of pure Atorvastatin and tablets ATR1 and ATR2

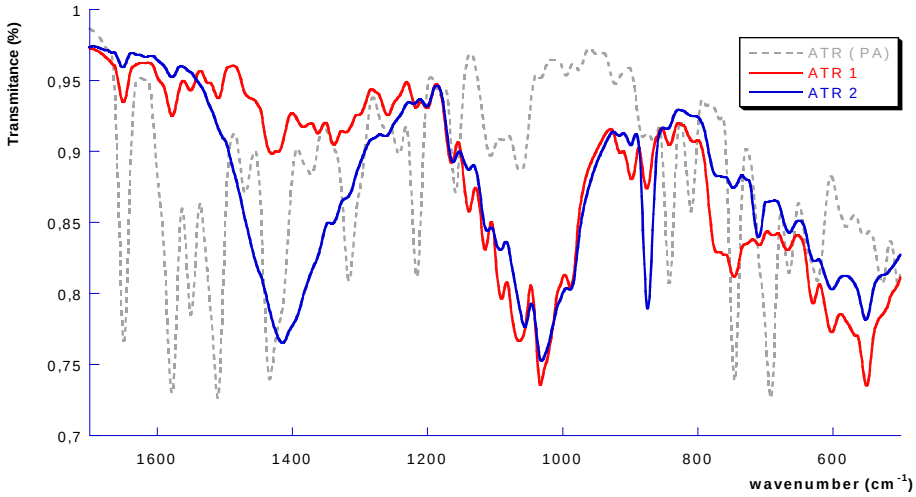

Fig.4 : FTIR spectra of pure atorvastatin and tablets ATR1 and ATR2

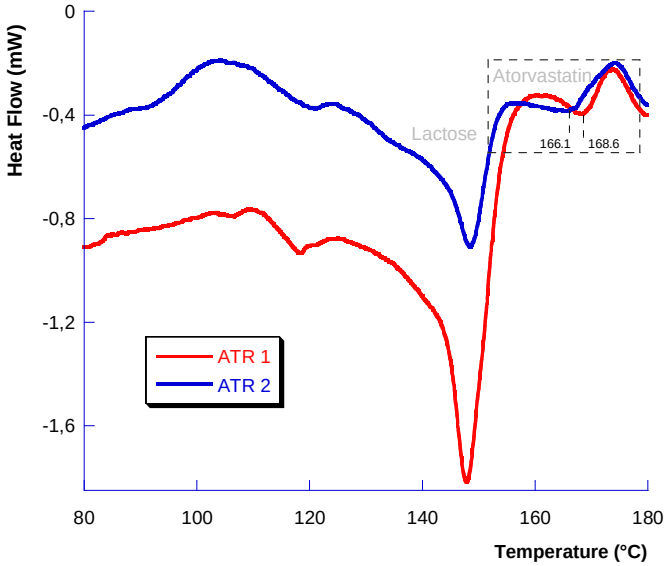

Fig.5: DSC curves of pure atorvastatin and tablets ATR1 and ATR2

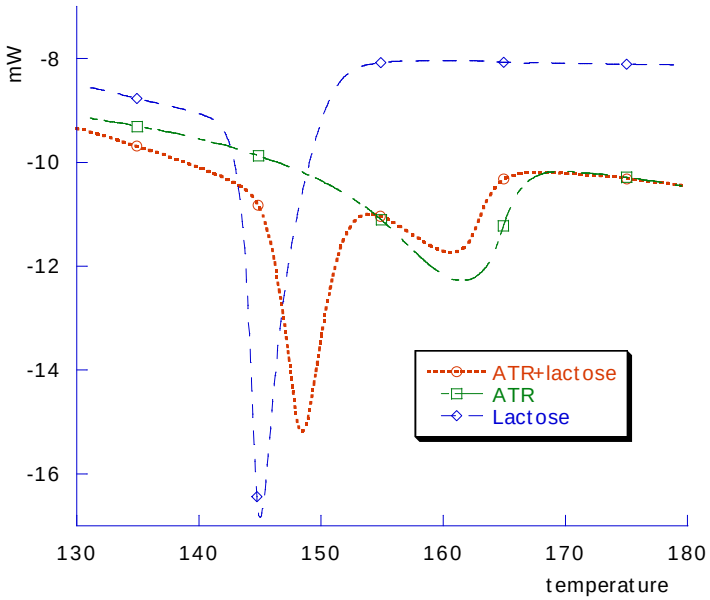

Fig.6 : DSC curves of atorvastatin and lactose and their 1:1 physical mixture

Dissolution curves (Fig.2) indicates that ATR1 shows a decrease in the extent of dissolution with respect to ATR2, particularly at the early time-points.

XRD patterns (Fig.3) show that only polymorphic form I is detected in both products. Moreover, no significant difference in the drug substance profile is shown by the FTIR analysis (Fig.4).

From the DSC curves, only a slight shift in the melting temperature was seen between the two samples ATR1 and ATR2 (fig.5). Furthermore, the replacement of calcium carbonate (ATR2) by lactose (ATR1) generates no incompatibility. In addition, no thermal interaction within the physical mixture of atorvastatin and lactose was shown by the DSC result (Fig. 6).

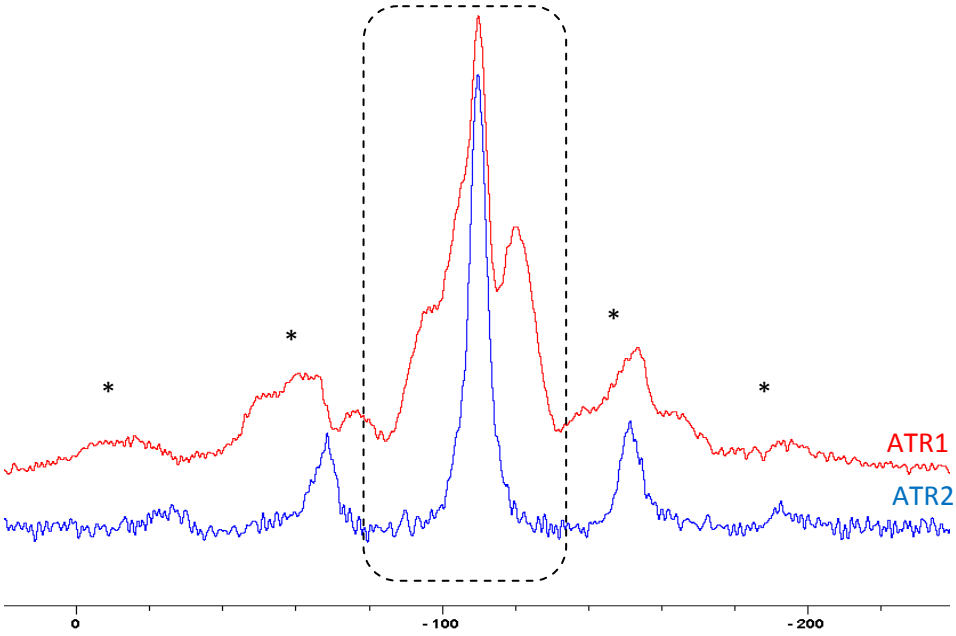

Fig.7 : 19 F MAS-NMR of pure atorvastatin and tablets ATR1 and ATR2, The spinning sidebands are indicated with "*"

Figure 7 shows the 19 F ssNMR spectra of ATR1 and ATR2. The central peak at -110 ppm should include two distinguishable resonances, indicating the two fluorine sites in ATC-I, as described by wang *et al* [20] and urbanova *et al* [21]. However, in our experiment, the spectra were recorded with a lower magnetic field (300Hz), therefore

only one central peak is seen, at -110 ppm. It is worth mentioning that chemical shifts of Atorvastatin in pure form (not presented here) and in pharmaceutical dosage form, ATR2, are indistinguishable. In contrast, in the case of ATR1, additional peaks appeared besides the central peak, providing evidence of presence of other forms of atorvastatin. The broad NMR signal on the left side (-95 ppm) could be attributed to the amorphous ones while the narrow NMR peak on the right side (-123 ppm) could be assigned to a crystalline forms in low quantities, to the extent that are not detected by XRD.

The emergence of these auxiliary forms probably occurred during the manufacture of the final dosage form which often involves high-energy processes, a high processing temperature and the use of water, which leads to solid-state transformations.

CONCLUSION

ssNMR 19 F spectroscopy was able to characterize the solid state forms of Atorvastatin in tablets despite the interference from the pharmaceutical additives. It was concluded that the tablet with a lower dissolution rate, presented many forms of Atorvastatin. Solid state NMR proved to be an essential tool to predict the impact of the solid state of a drug substance on its bioavailability.

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