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A Stable Amorphous Statin: Solid-State NMR and Dielectric Studies on Dynamic Heterogeneity of Simvastatin

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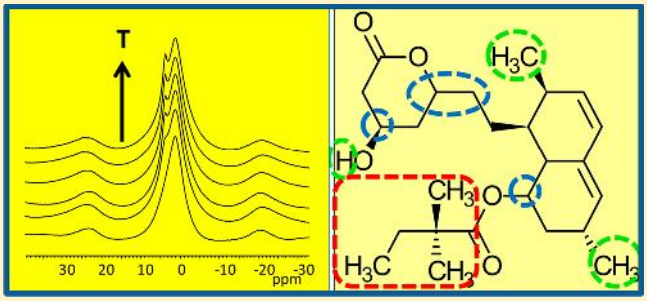
ABSTRACT: Statins have been widely used as cholesterol-lowering agents. However, low aqueous solubility of crystalline statins and, consequently, reduced biovailability require seeking for alternative forms and formulations to ensure an accurate therapeutic window. The objective of the present study was to evaluate the stability of amorphous simvastatin by probing molecular dynamics using two nondestructive techniques: solid-state NMR and dielectric relaxation spectroscopy. Glassy simvastatin was obtained by the melt quench technique. ^{13}C cross-polarization/magic-angle-spinning (CP/MAS) NMR spectra and ^{1}H MAS NMR spectra were obtained from 293 K up to 333 K ($T_g \approx 302$ K). The ^{13}C spin−lattice relaxation times in the rotating frame, $T_{1\rho}$, were measured as a function of temperature, and the correlation time and activation energy data obtained for local motions in different frequency scales revealed strong dynamic heterogeneity, which appears to be essential for the stability of the amorphous form of simvastatin. In addition, the ^{1}H MAS measurements presented evidence for mobility of the hydrogen atoms in hydroxyl groups which was assigned to noncooperative secondary relaxations. The complex dielectric permittivity of simvastatin was monitored in isochronal mode at five frequencies (from 0.1 to 1000 kHz), by carrying out a heating/cooling cycle allowing to obtain simvastatin in the supercooled and glassy states. The results showed that no dipolar moment was lost due to immobilization, thus confirming that no crystallization had taken place. Complementarily, the present study focused on the thermal stability of simvastatin using thermogravimetric analysis while the thermal events were followed up by differential scanning calorimetry and dielectric relaxation spectroscopy. Overall, the results confirm that the simvastatin in the glass form reveals a potential use in the solid phase formulation on the pharmaceutical industry.



KEYWORDS: *amorphous simvastatin, solid-state NMR, DSC, TGA, DRS*

1. INTRODUCTION

The growing number of active pharmaceutical ingredients (APIs) with poor aqueous solubility has led to development of various strategies to improve dissolution rates. The transformation from their crystalline state to a more soluble amorphous, nanocrystalline solid dispersion and/or solid solution represents the most promising ways as the bioavailability of APIs depends on solubility in human fluids and permeability in the gastrointestinal tract.[1] As the amorphous form of drugs is thermodynamically less stable than their crystalline counterparts, different methods for stabilization of these forms are emerging to profit from their solubility and dissolution rate advantages.[2] Hence, a detailed solid-state study can be very useful to predict any structural changes that may influence the drug properties,[3] for example, the increase of their shelf-life time.

To characterize pharmaceutical solids, we may use various techniques. Spectroscopic techniques such as Fourier transform Raman spectroscopy (FT-RS), Fourier transform infrared spectroscopy (FT-IR), and solid-state nuclear magnetic resonance spectroscopy (ss-NMR) are primarily intramolecular methods, probing the sample at the molecular level. Intermolecular information is gained by directly employing

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