Journal of Non-Crystalline Solids 550 (2020) 120407

Contents lists available at ScienceDirect

Journal of Non-Crystalline Solids

journal homepage: www.elsevier.com/locate/jnoncrysol

Molecular dynamics in the supercooled liquid and glassy states of bezafibrate and binary mixture of fenofibrate

Aboothahir Afzal[a,b], Mohamed Shahin Thayyil[a,*], P.A. Sivaramakrishnan[b], Sailaja Urpayil[c], Simone Capaccioli[d]

[a] Department of Physics, University of Calicut, Kerala, India
[b] Department of Physics, Govt. Arts and Science College, Kozhikode, Kerala, India
[c] Department of Physics, MES Keveeyam College, Valanchery, Malappuram, Kerala, India
[d] Dipartimento di Fisica - Università di Pisa, Pisa, Italy

ARTICLE INFO

Keywords:
Amorphous pharmaceuticals
Glass transition
Broadband dielectric spectroscopy
Poorly soluble drugs
Molecular dynamics
Density functional theory

ABSTRACT

Two solubility limited pharmaceuticals bezafibrate and fenofibrate, belonging to BCS class II drugs, were compared, by investigating molecular dynamics of the former and compared with the neat and as a probe in an apolar host polystyrene of mole. wt. 800 (PS800) of the latter by broadband dielectric spectroscopy (BDS), other supporting thermal and spectroscopic experimental means and density functional theory (DFT) calculations. The BDS experiments from frozen glassy state to vibrant molten state of the title drugs were done to explore the role of parameters describing their complex molecular dynamics and the stabiliy of amorphous phase, such as glass transition temperature (T_g), temperature dependence of α-relaxation times (τ_α), width of structural dispersion and its role on the occurrence of Johari-Goldstein (JG) β-relaxation, fragility index (m) and apparent activation energy of secondary processes. Realizing that most of the pharmaceuticals have narrow α-dispersion which limits the visibility of JG β-relaxation as a separate process in the dielectric window, to resolve the conundrum, we have further explored the amorphous dynamics of fenofibrate as a probein an apolar host polystyrene of molecular weight 800 (PS800) having higher T_g than the polar probe. The T_g of bezafibrate and PS800-fenofibrate mixture were determined to be 298 K and 275 K respectively, whereas the fractional exponent of Kohlrausch–Williams–Watts function β_{KWW} of bezafibrate was determined to be 0.68 which is closer to that of fenofibrate, whereas that of PS800-fenofibrate mixture was found to be much broader with a value of 0.39, all in the vicinity of T_g. Even though β_{KWW} decreased in binary mixture of fenofibrate when compared to its pure form due to concentration fluctuations and other aspects, but cold crystallization tendency was absent and T_g is elevated than that of fenofibrate. Due to higher T_g than that of fenofibrate, amorphous bezafibrate is more stable than fenofibrate. Finally, using quantum computational calculations using DFT, the relevant flexible parts of the two drug molecules, whose motions manifests the secondary γ-relaxation was identified by calculating potential energy barriers and dipole moments on relaxed dihedral angle scans, as no experimental technique is available for this purpose.

1. Introduction

Ensuring solubility and permeability is the Herculean task, an active pharmaceutical ingredient (API) for oral delivery has to accomplish for getting efficient absorption and optimal therapeutic application [1,2]. Despite various strategies and intelligent protocols to enhance the bioavailability, a good number API's fail to fulfill this test, mainly due to poor water solubility, according to the bio-pharmaceutics classification system (BCS) [3,4], and hence the improvement of drug solubility is one of the prominent aspects of drug development process [3,5]. The severity of the situation can be read from the fact that about 40% of drugs wait for the market approval, and 90% of molecules in the drug discovery pipeline are poorly water-soluble [6–8]. Realizing the situation, different solubility enhancement tactics are already in practice, on modifying the API' via physical and chemical routes without losing its potency. Among these, amorphous formulation of poorly water-soluble drugs, and their stabilization, has become a promising approach [9], which can provide significant improvements in the solubility, to attain enhanced bioavailability vis-à-vis to their crystalline counterparts when administered orally [10]. However, all the accomplished benefits from

* Corresponding author: Mohamed Shahin Thayyil, Department of Physics, Calicut University, Malappuram district, Kerala, India.
E-mail address: shahin@uoc.ac.in (M.S. Thayyil).

https://doi.org/10.1016/j.jnoncrysol.2020.120407
Received 15 June 2020; Received in revised form 31 August 2020; Accepted 2 September 2020