
WELCOME.....

Relaxation dynamics of amorphous pharmaceuticals

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Motivation

Drug administration is better in the amorphous state than in the crystalline state. But shelf-life of the amorphous drugs are low because there is a greater chance for crystallization due to the molecular mobility present in the amorphous state.

Aim

To investigate different relaxation processes present in the amorphous pharmaceuticals and their role in the crystallization of drugs. Apply this to design amorphous drugs having better solubility, bioavailability and longer shelf-life.

Objective

To investigate different relaxation processes (dielectric properties) present in glass-forming pharmaceuticals by BDS.



INTRODUCTION

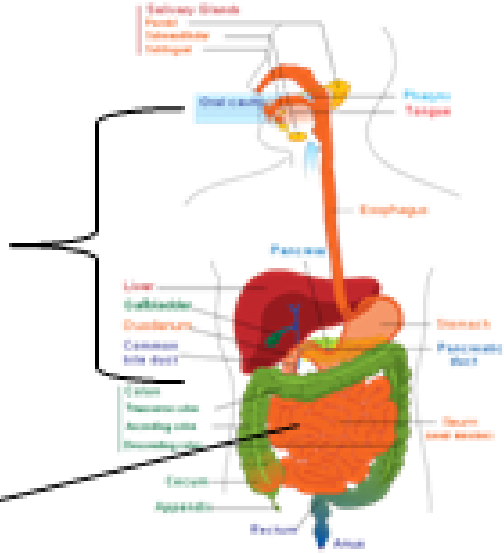
Background4Christian.com

amorphous pharmaceuticals

orally delivered API has to overcome two huddles successfully

solubility

mixing of the drug with elementary canal fluids (mouth to intestine)



permeability

drug has to permeate from elementary canal to blood stream

Amorphous pharmaceuticals

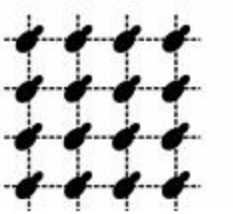
API are classified accordingly

	I	*II*	*III*	*IV*
solubility	***high***	***high***	***low***	***low***
permeability	***high***	***low***	***high***	***low***

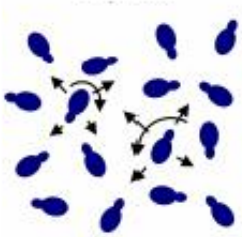
***amorphous route** can give improved solubility for water insoluble solid APIs*

Amorphous pharmaceuticals

mixing of solid API in the oral route

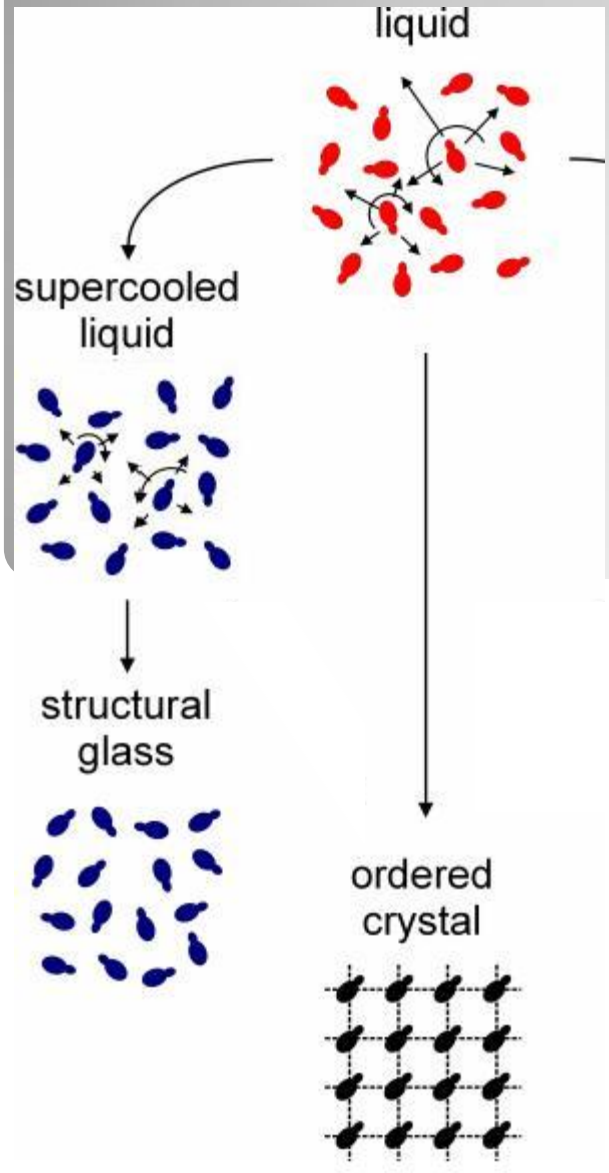


mixing – escape of individual molecule from the Madelung bond of crystalline API. Getting energy to overcome this barrier from thermal fluctuations is less probable.

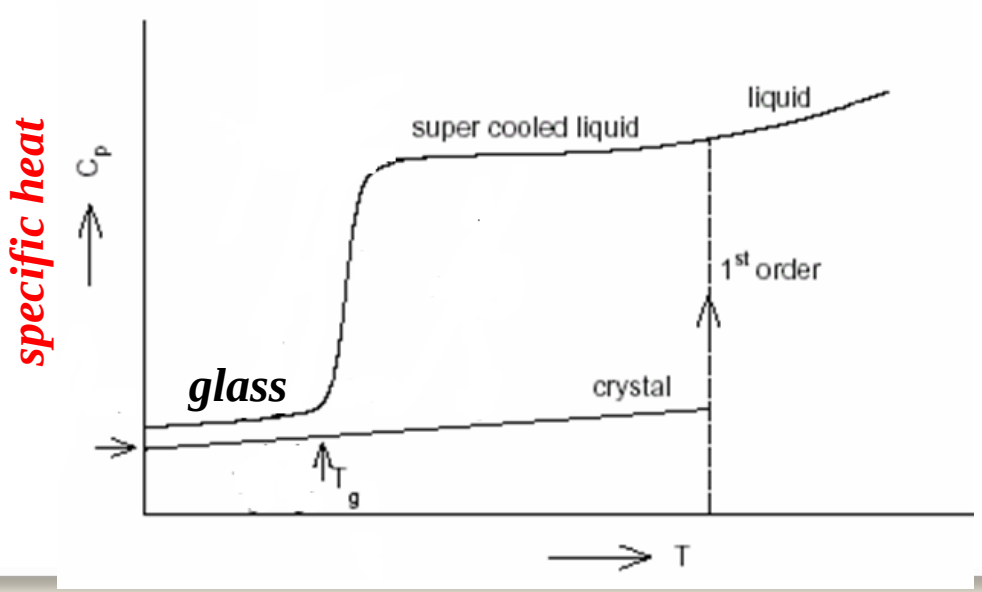


amorphous state –only very weak van der Waal's interaction. molecules are at higher free energy. Hence can mix better and quicker

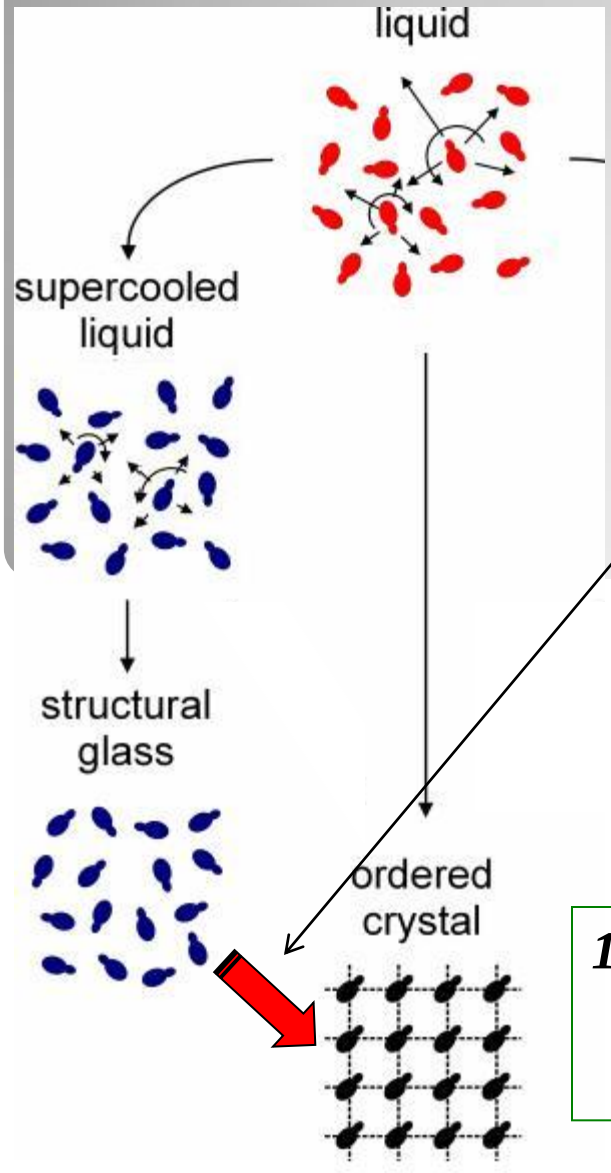
Vitrification of solid API



cooling faster** can bypass this ordering to **retain disorder** and reach **glassy state



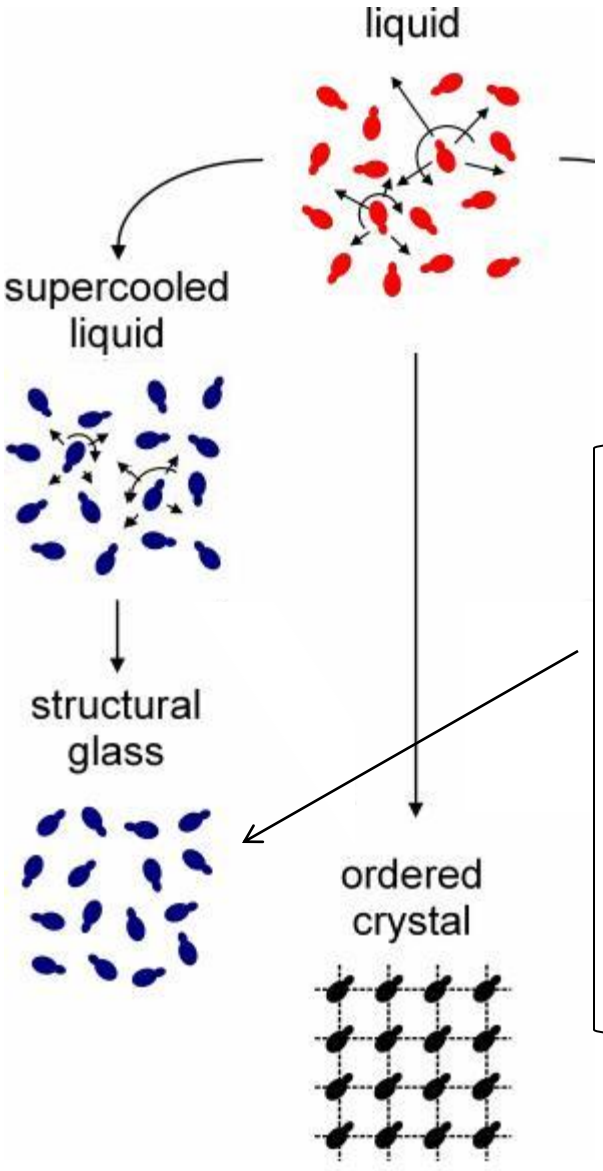
Vitrification of API – issues to be addressed



amorphous API can gradually transform to crystalline phase

100 s & above	***100 s – 10^{-9}***	***10^{-9} and lower***
Glass	***supercooled liquid***	***liquid***

Vitrification of API – issues to be addressed



amorphous API can gradually transform to crystalline phase

shelf-life needed is more than 2 years

stability of API against degradation is yet to be systematically investigated.

systematic investigation is needed for taking this to application front.

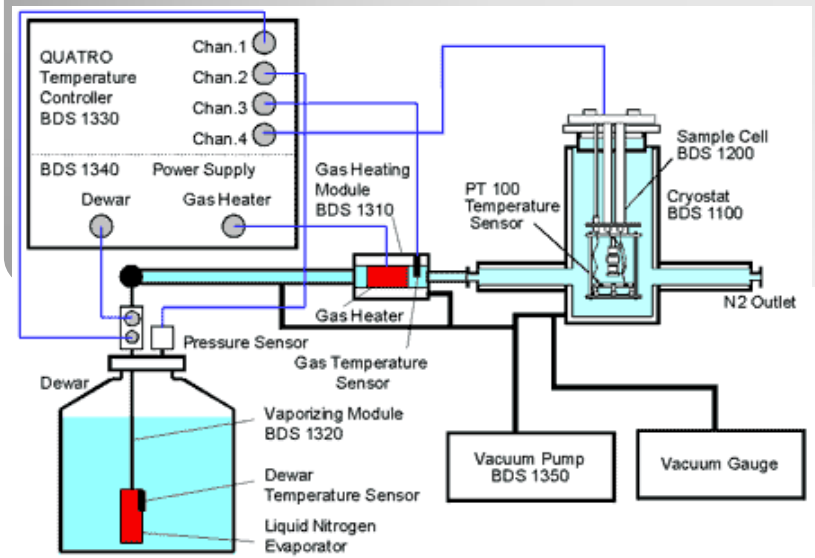


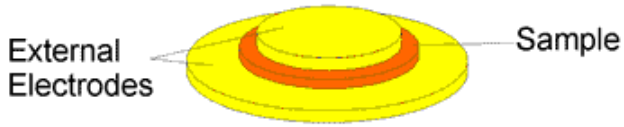
DIELECTRIC RELAXATION STUDIES

Theory:

The polarization studied by dielectric spectroscopy is the orientational polarizability which is due to dipole relaxation. The important function that is measured from dielectric spectroscopy is the complex dielectric function $\varepsilon^*(\omega)=\varepsilon'(\omega)-i\varepsilon''(\omega)$ (ε'-real part, ε''-imaginary or loss part).

Broadband dielectric spectrometer Novocontrol (10^{-3} -10^{7} Hz)





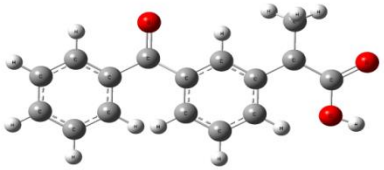


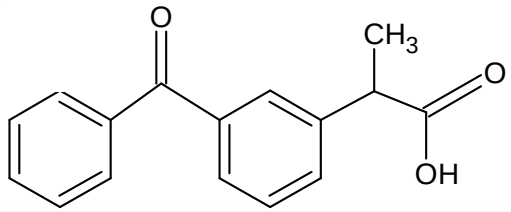
Data analysis

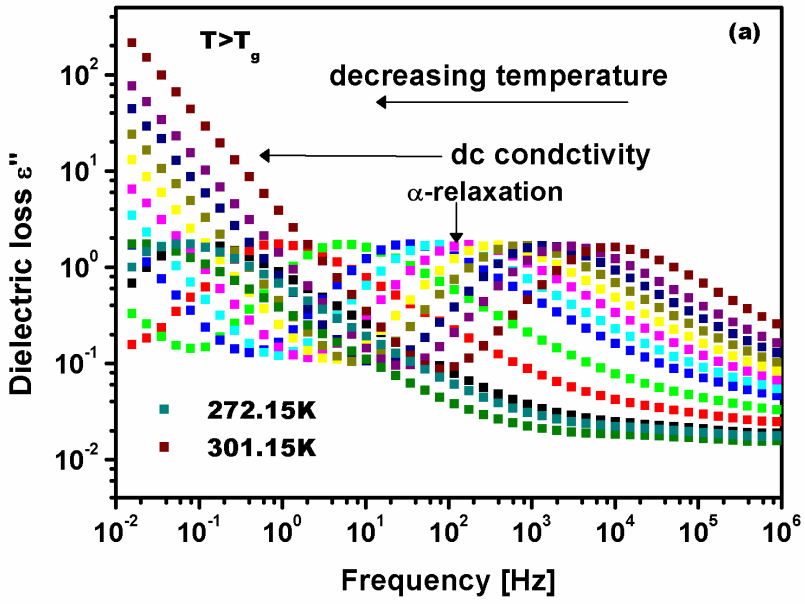
- *The analysis time was 18 hours in BDS*
- *Frequency range is between 10^{-2} to 10^{7} Hz*
- *Temperature range is from -150 to 100 degree*
- *The spectra is analyzed by using Win-fit software*
- *Frequency corresponding to maximum dielectric loss in alpha process can be represented in Arrhenius diagram*
- *VFT Fit is done for alpha process to calculate Tg and fragility(m) and T_0*

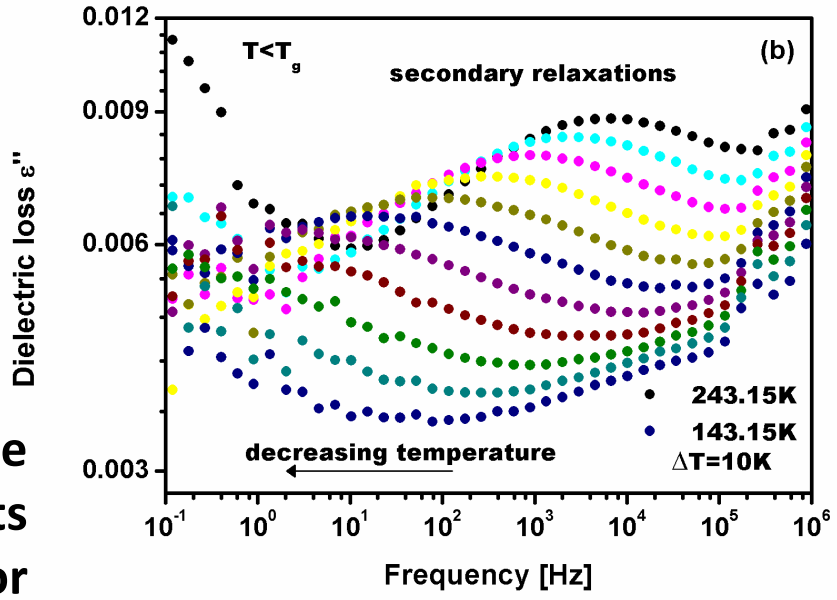
Ketoprofen

(Orudis/Oruvail)





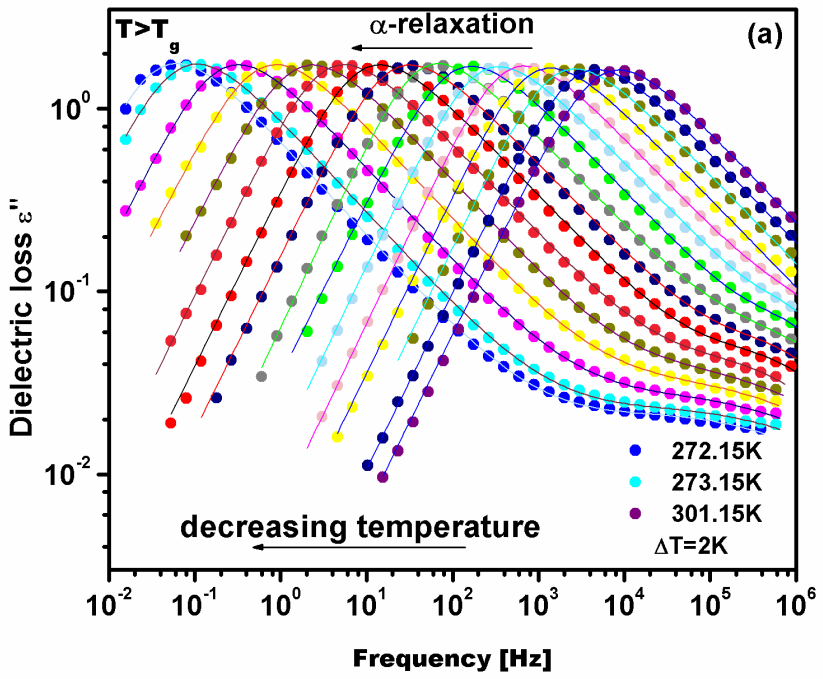


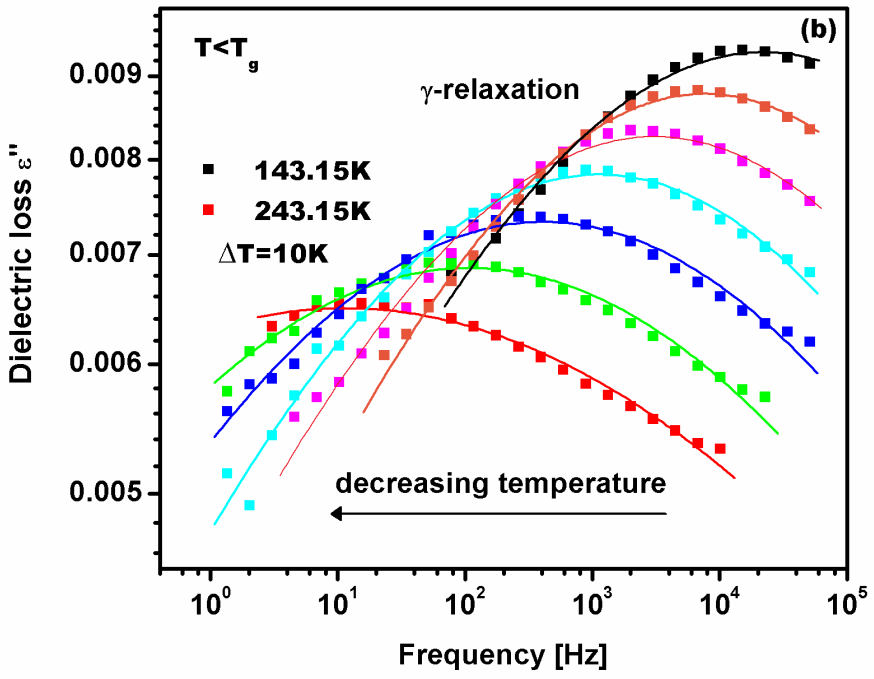


From 291.15 K (18degree) onwards the dielectric strength of *α*-process starts decreasing shows tendency for crystallization of ketoprofen.

Dielectric loss curves obtained for ketoprofen during heating

U. Sailaja et al, Eur. J. Pharm.Sci, 49 (2013)



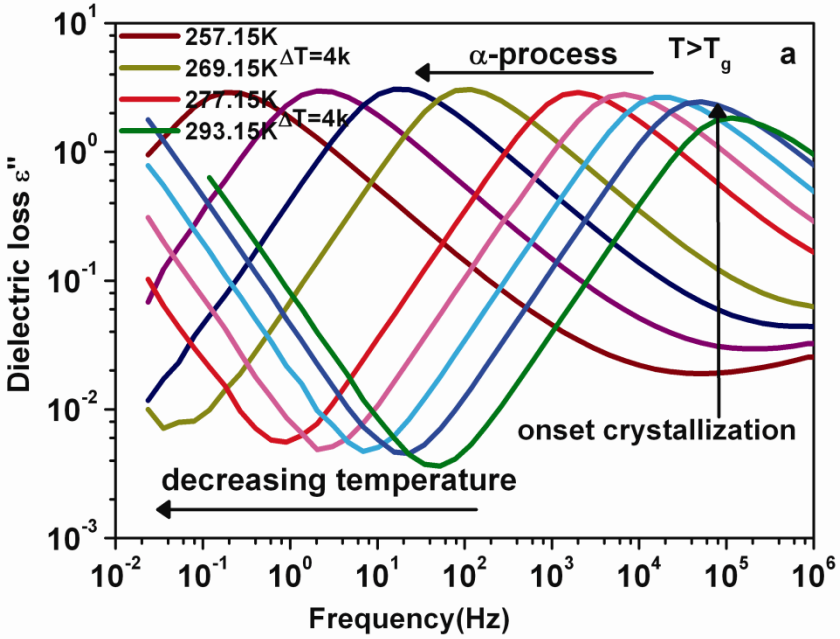


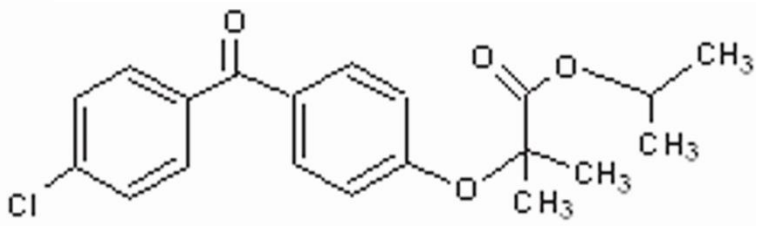
$$\varepsilon^*(\omega) = \varepsilon' - i\varepsilon'' = -i\left(\frac{\sigma_0}{\varepsilon_0\omega}\right)^N + \left[\varepsilon_\infty + \sum_k \left(\frac{\Delta\varepsilon}{\left(1+\left(i\omega\tau_{HNk}\right)^{\alpha_{HNk}}\right)^{\beta_{HNk}}}\right)\right]$$

HN fitted curves

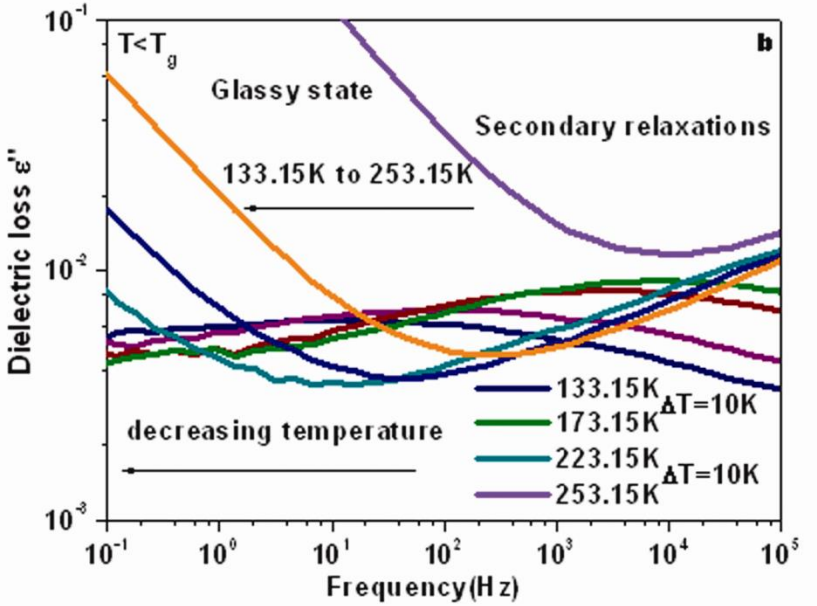
U. Sailaja et al, Eur. J. Pharm.Sci 49 2013

Fenofibrate



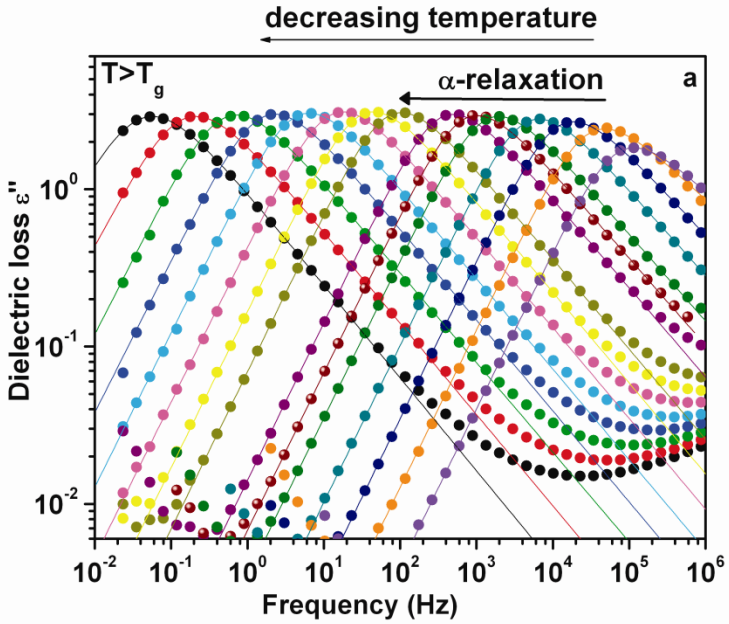


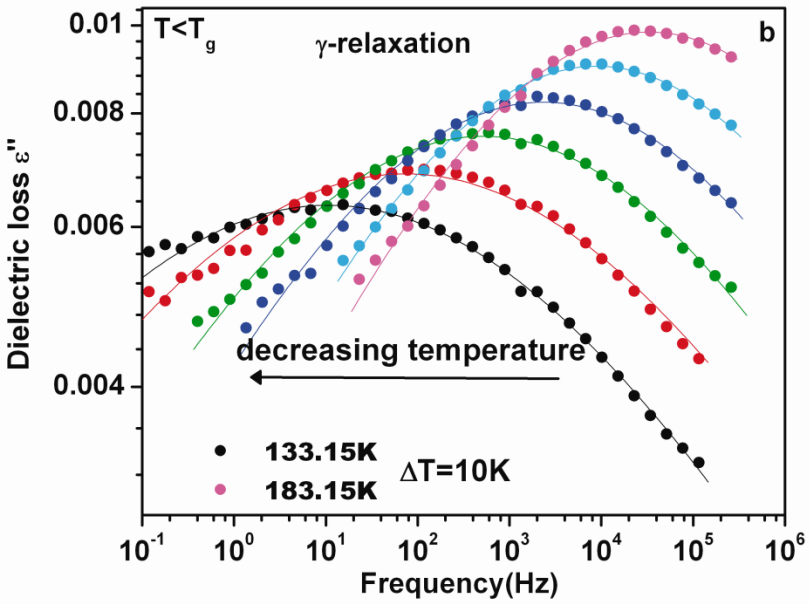
Primary relaxation above T_g

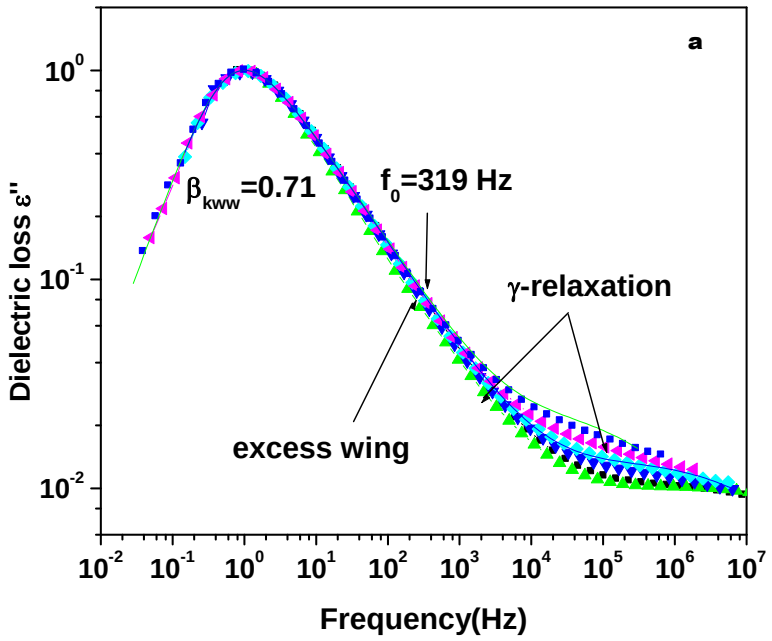


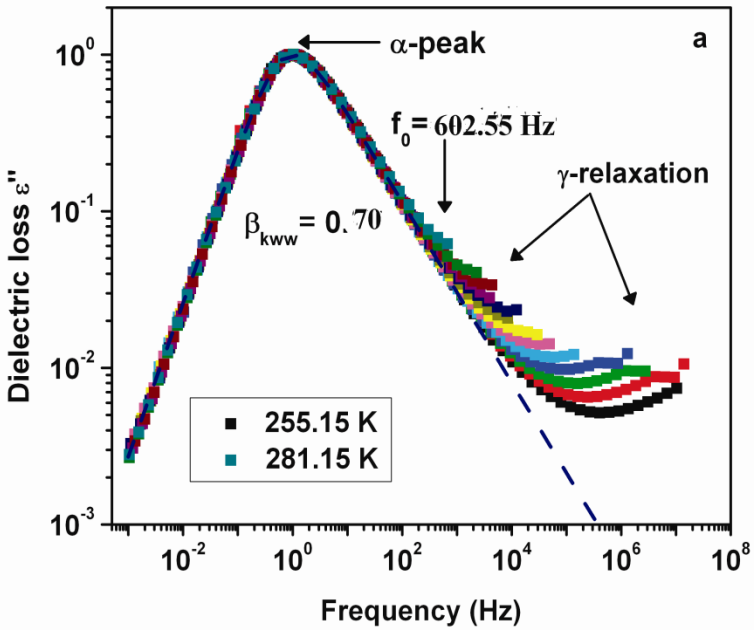
Secondary relaxation below T_g.

HN fitted Spectra of Fenofibrate







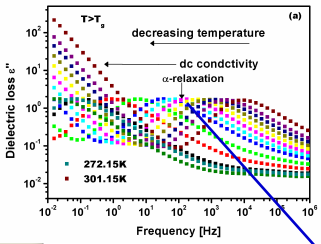


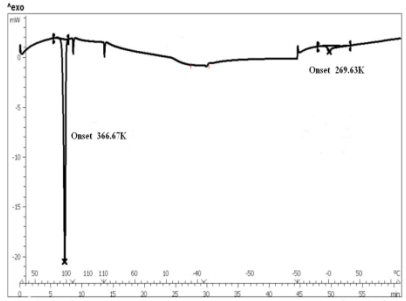
Master plot of ketoprofen formed by shifting several spectra near T_g to overlap the spectrum at 273.15K

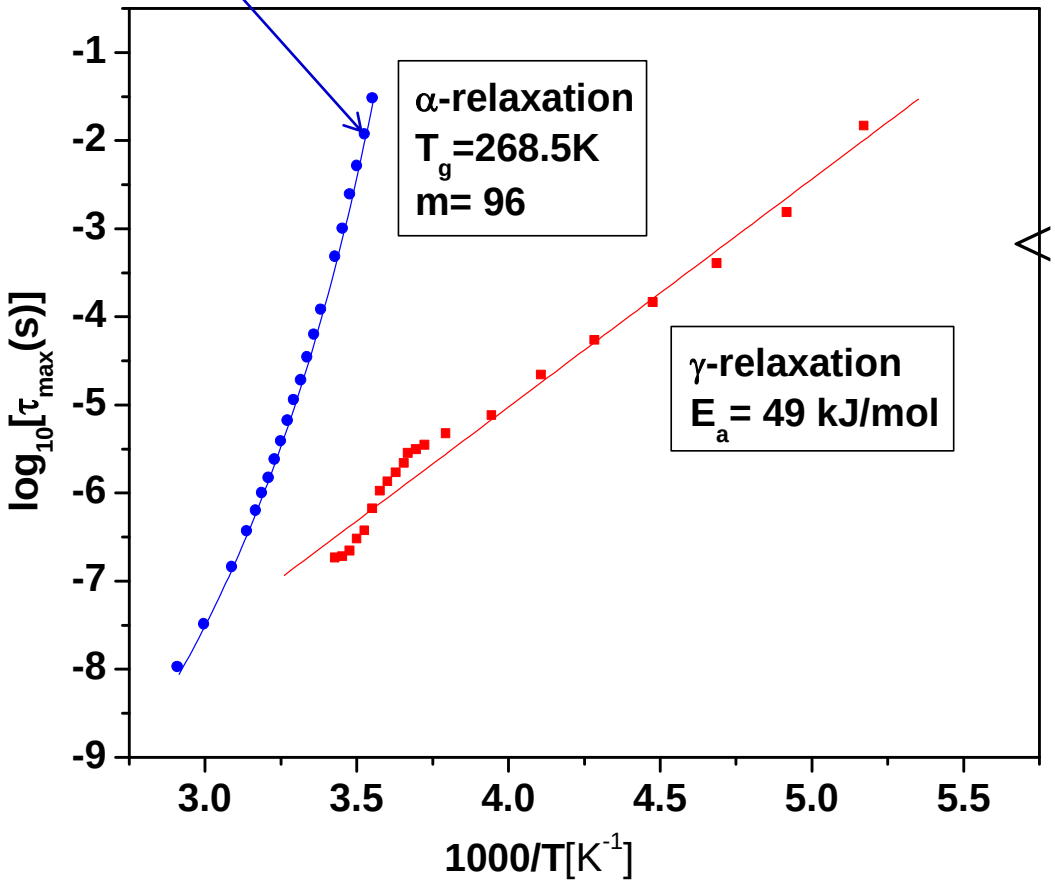
Tramadol monohydrate (Kaminski 2010)
Glibenclamide (Wojnarowska 2010)

U. Sailaja et al, Eur. J. Pharm.Sci 49 2013

Relaxation map of ketoprofen







$$< \tau >= \tau_{VF} \exp\left[B/\left(T - T_0\right)\right]$$

$$m = \frac{d \log_{10} \tau_\alpha}{d\left(\frac{T_g}{T}\right)} / T = T_g$$

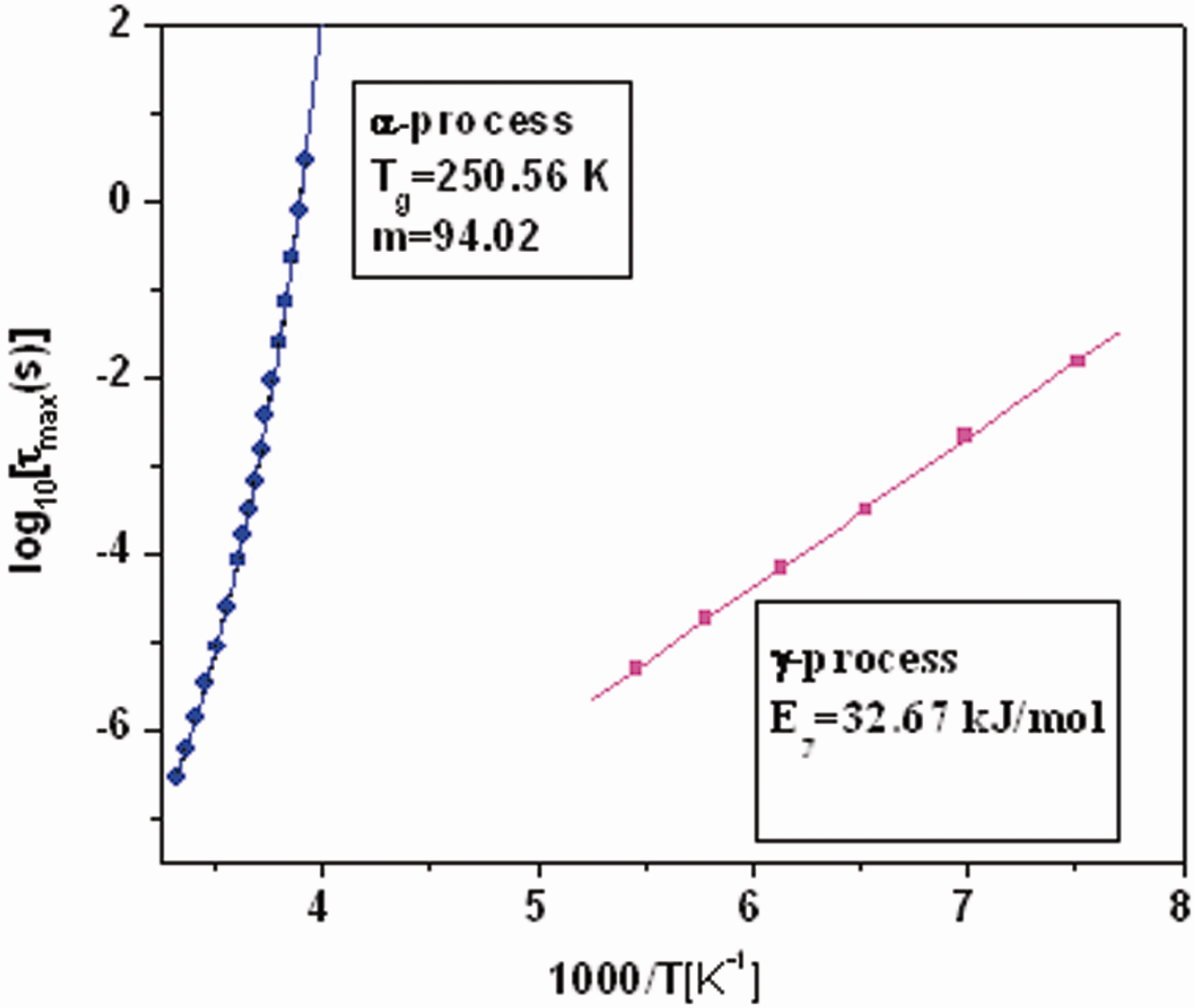
$$\tau\left(T\right) = \tau_\infty \exp\left(\frac{E_a}{RT}\right)$$

T_0 = 222K (Hancock1997)

Yu et al., 2001, pointed out that if m < 45 they belong to strong and if m > 75 the liquids belongs to fragile group

U. Sailaja et al, Eur. J. Pharm.Sci 49 2013

Relaxation map of Fenofibrate



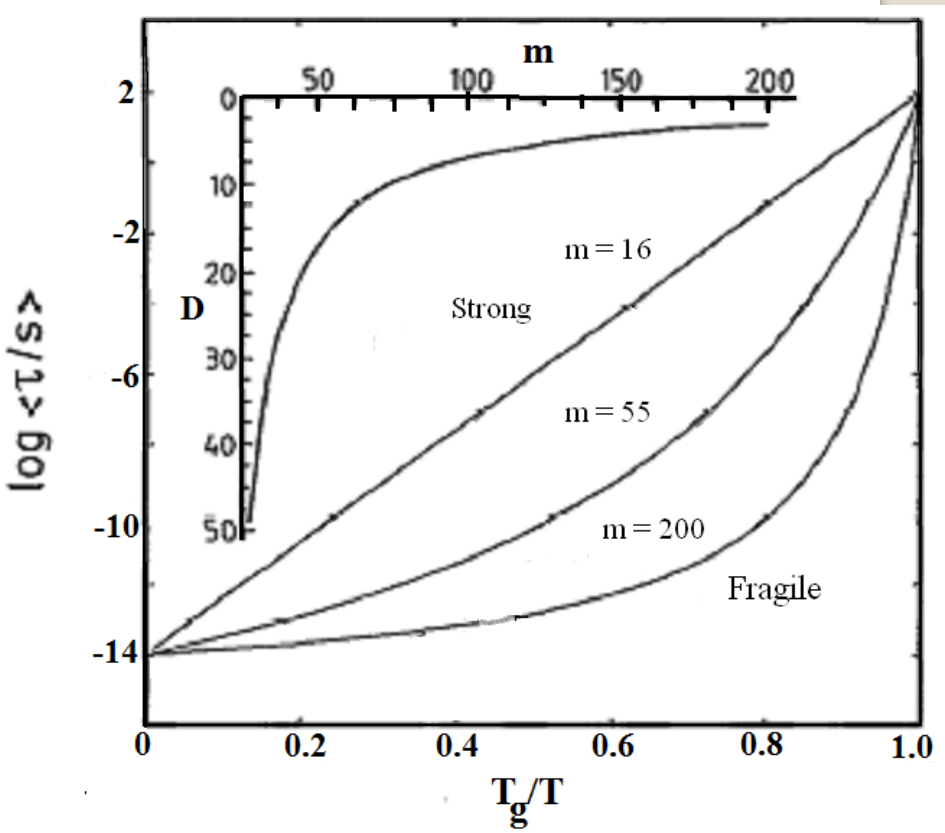
Strong and fragile glasses

Strong systems*: *Strong resistance against structural degradation

Fragile systems*: *Shows large deviation from Arrhenius law

VFT equation

$$\langle\tau\rangle = \tau_{VF} \exp[B/(T - T_0)]$$



m=16, 200

Angell, C.A. 1991

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Molecular dynamics in liquid and glassy states of non-steroidal anti-inflammatory drug: Ketoprofen

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ABSTRACT

Ketoprofen is a well known nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin. The molecular mobility of amorphous ketoprofen has been investigated by broadband dielectric spectroscopy (BDS) covering wide temperature and frequency range. Multiple relaxation processes were observed. Besides the primary α-relaxation, one secondary relaxation, γ-have been identified. The γ-process visible in the dielectric spectra at very low temperature is non-JG relaxation, and has an activation energy $E = 37.91$ kJ/mol typical for local mobility. Based on Ngai's coupling model smaller n or a larger Kohlrausch exponent $(1 - n)$ of the α-relaxation associated with larger τ_β (T_g). In the case of ketoprofen we conclude that the secondary relaxation (β) emerging from intermolecular motions, is hidden under the dominant α-peak. The temperature dependence of the relaxation time of the α-process can be described over the entire measured range by a single Vogel–Fulcher–Tammann (VFT) equation. From VFT fits, the glass transition temperature (T_g) was estimated as 267.07 K, and a fragility or steepness index $m = 86.57$ was calculated, showing that ketoprofen is a fragile glass former. Our differential scanning calorimetry (DSC) study shows that ketoprofen is a non-crystallizing compound. To confirm the hydrogen bond patterns of ketoprofen FTIR spectroscopy was applied in both crystalline and amorphous phases. Solubility test performed at 37 °C proved that amorphous phase is more soluble than the crystalline phase.

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1. Introduction

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin (Tripathi, 2008). Among the pharmaceutical drugs about 40% are found to be poorly water soluble, which results in inadequate bioavailability (Lipinski, 2002). In order to induce the effect of the drug fully, the dose of the used drug will be kept in higher level during manufacturing. To improve the bioavailability and solubility of active pharmaceutical ingredients (APIs) is a challenging task of a pharmaceutical scientist. Dantuluri et al., pointed out that nanocrystalline solid dispersion (NCSD) is a best alternative for poorly water soluble drugs. NCSDs can be prepared by annealing of amorphous solid dispersion to increase the solubility and bioavailability (Dantuluri et al., 2011; equivalent; they have high internal energy, enthalpy and specific volume. Because of these reasons they have enhanced dissolution rate and bioavailability, but their higher molecular mobility will reduce the shelf life of the amorphous drug during processing and storage i.e., there is greater tendency for devitrification of the drug (Alie et al., 2003; Gupta and Bansal, 2005; Yu, 2001; Makower and Dye, 1956). Moreover it is easier to make tablets out of amorphous pharmaceuticals and can avoid the use of excipients, which is used for making the drugs into tablet form (Kaminski et al., 2010).

Recent reports shows that molecular mobility is responsible for the instability of the amorphous phase (Aso et al., 2000; Bhugra and Pikal, 2007; Grzybowska et al., 2010; Shamblin et al., 1999; Zhou et al., 2002). Significant amount of molecular mobility has

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Original Article

Molecular dynamics of amorphous pharmaceutical fenofibrate studied by broadband dielectric spectroscopy ☆

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ABSTRACT

Fenofibrate is mainly used to reduce cholesterol level in patients at risk for cardiovascular disease. Thermal transition study with the help of differential scanning calorimetry (DSC) shows that the aforesaid active pharmaceutical ingredient (API) is a good glass former. Based on our DSC study, the molecular dynamics of this API has been carried out by broadband dielectric spectroscopy (BDS) covering wide temperature and frequency ranges. Dielectric measurements of amorphous fenofibrate were performed after its vitrification by fast cooling from a few degrees above the melting point ($T_m = 354.11$ K) to deep glassy state. The sample does not show any crystallization tendency during cooling and reaches it in the glassy state. The temperature dependence of the structural relaxation has been fitted by single Vogel–Fulcher–Tamman (VFT) equation. From VFT fit, glass transition temperature (T_g) was estimated as 250.56 K and fragility (m) was determined as 94.02. This drug is classified as a fragile glass former. Deviations of experimental data from Kohlrausch–Williams–Watts (KWW) fits on high-frequency flank of α-peak indicate the presence of an excess wing in fenofibrate. Based on Ngai's coupling model, we identified the excess wing as true Johari–Goldstein (JG) process. Below the glass transition temperature one can clearly see a secondary relaxation (γ) with an activation energy of 32.67 kJ/mol.
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1. Introduction

To increase the solubility and bioavailability of the poorly water soluble crystalline drugs is a challenge to modern pharmaceutical scientists. One of the promising methods for improving solubility and bioavailability of poorly water soluble crystalline drugs is to prepare them in the amorphous form. Amorphous form of pharmacologically active materials is very important because this form has enhanced thermodynamic properties, having high internal energy, solubility, bioavailability, dissolution rate, better compression characteristics and greater therapeutic activity than the corresponding crystalline counterpart [1–4]. However, amorphous systems are physically and chemically unstable and therefore show crystallization tendencies.

Recent studies on various amorphous pharmaceutical drugs show that molecular mobility above and below the glass transition temperature (T_g) plays an important role in the devitrification of the drugs. The knowledge about the molecular dynamics of the drugs in the amorphous phase is very important for safety storage in order to obtain the maximum shelf-life and stability [5–8].

Fenofibrate had been chosen as a model drug for the current study. It is a fibric acid derivative which has greater HDL-CH (high density lipoprotein cholesterol) rising and greater LDL-CH (low density lipoprotein cholesterol) lowering action than other fibrates [9]. To the best of our knowledge, this will be the first attempt to describe the dielectric relaxation study of amorphous fenofibrate.

For this it is essential to have a better understanding of molecular dynamics in supercooled and glassy state of this API. In the present study, we used differential scanning calorimetry (DSC) for thermal transition analysis and observed that fenofibrate is a very good glass former. Based on DSC study, dielectric measurements of this API were carried out by broadband dielectric spectroscopy (BDS) as an investigative tool to study the molecular dynamics of amorphous systems in a wide range of frequencies ($f = 10^9$–10^{-2} Hz) at different thermodynamic conditions (P, T). Recently this technique has been successfully applied to study the molecular dynamics of various amorphous pharmaceuticals [10–12]. To get a clear picture of hydrogen bonding in the crystalline and amorphous state of fenofibrate infrared (IR) spectroscopy was used.

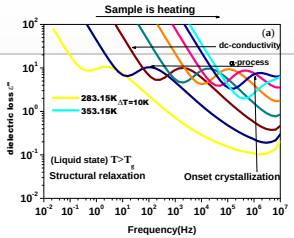
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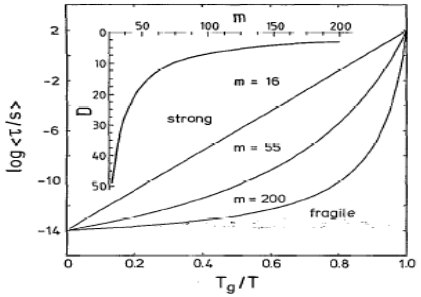
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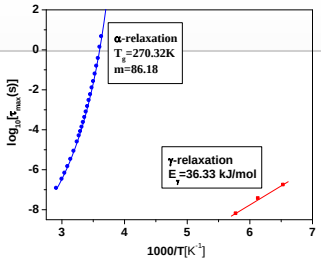
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Band
Opacity
100%
CONCLUSIONS









Dielectric studies: **Molecular mobility is found to be responsible for the crystallization of the APIs and JG relaxation is one of the main reasons for devitrification and found to universal. To prevent devitrification of the drugs we have to understand the complete factors responsible for devtrification so that the drugs can attain maximum shelf-life in the amorphous form.**

Binary mixture of these APIs with different excipients can be done to check the miscibility of the drugs and thereby avoiding crystallization during processing, handling and storage in the amorphous phase for getting maximum shelf-life and stability.

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