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The Vibrational Behavior of the Mixture Quercetin/Gelucire 50/13 at Room and Body Temperature

M. El Hadri[1], B. Khelifa[2,5], V. Faivre[3], O. Abbas[4] and S. Bresson[5]

1. Laboratory of Condensed Matter Physics, Abdelmalek Essaâdi University, Tetouan 93000, Morocco

2. Faculty of Science, University of Artois, Lens 62300, France

3. Polyphase Systems Physical Chemistry Team, UMR CNRS 8612, Labex LERMIT, University of Paris Sud, Paris 75000, France

4. Walloon Agricultural Research Centre (CRA-W), Valorisation of Agricultural Products, Department, Food and Feed Quality Unit (U15), Gembloux 5030, Belgium

5. Institut Polytechnique UniLaSalle, Université d'Artois, ULR 7519, 19 Rue Pierre Waguet, BP 30313, Beauvais 60026, France

Abstract: The present paper discusses the vibrational properties of the mixture gelucire-quercetin (from 1% to 5%) at room and body temperature. Quercetin is a flavonoid having beneficial properties: biological and antioxidant; it is used in many fields as food, cosmetic and especially pharmaceutics but its use as a drug is affected by its low solubility. The Gelucire 50/13 is used as sustained release matrix forming agent in pharmaceutical applications and it has demonstrated the ability to improve the dissolution as well as the absorption of poorly water-soluble drugs. The mixture Gelucire-quercetin was essentially studied by FTIR (Fourier transform infrared spectroscopy) and Raman spectroscopy. The behavior of these two molecules has been investigated in the spectral range 4000-0 cm^{-1} in Raman spectroscopy, and 4,000-600 cm^{-1} in FTIR.

Key words: Gelucire 50/13, quercetin, solubility, Raman spectroscopy, IR spectroscopy.

1. Introduction

Quercetin is a flavonoid that has been the subject of dozens of scientific reports over the past thirty years. Itseems to have multiple beneficial effects on humanhealth, including cardiovascular protection, anti-cancer activity, anti-ulcer effects, antiallergic activity, antiviral and anti-inflammatory, but its use as a drug is affected by its low solubility in the formulation milieu, and its instability to light and heat. To solve these problems we used the excipient Gelucire 50/13 (the two numbers correspond, respectively, to the fusion point and the hydrophilic-lipophilic balance value or HLB). Gelucire 50/13 is an amphiphilic compound, uncharged and capable of reducing the surface tension between an aqueous phase and an organic phase, it consists of a mix of mono-, di-, triacyl glycerol (around 20% in weight) and monoacyl polyoxyethylene glycols and diacyl polyoxyethyleneglycols labeled, respectively, MPEG and DPEG (72%), and 8% of PEG (polyoxyethylene glycols) [1-4].Despite the dozens of existing studies that examined the different crystal structures of quercetin alone and Gelucire alone, there is a lack of information on the influence of mixing Gelucire with quercetin on the physicochemical properties of the quercetin. For this reason, the objective of this study is to characterize the mixture quercetin-Gelucire 50/13 at room and body temperature, using Raman and IR spectroscopy to determine their physicochemical properties and especially their solubility and the influence of Gelucire 50/13 on the quercetin dihydrate.

Corresponding author: Mustapha El Hadri, assistant professor, research fields: condensed matter physics.

2. Experimental and Computational Details

2.1 Preparation of the Gelucire 50/13

Small pellets of Gelucire 50/13 were supplied by Gattefossé S. A. S., St Priest (France), and were analyzed without any special thermal treatment (as received). Gelucire 50/13 is synthesized by an alcoholysis/esterification reaction using as starting materials hydrogenated palm oil and PEG 1500, equivalent to approximately 34 monomer units $-CH_2-CH_2-O-$, and ended by two alcohol groups.

2.2 FT-Raman and FT-IR Spectroscopy

The FT-Raman and FTIR measurements were realised in the Walloon Agricultural Research Centre (CRA-W). FT-Raman and FTIR spectra were acquired on a Bruker RAM II spectrometer coupled with Vertex 70 ATR-FTIR spectrometer. This instrument is equipped with a Nd:YAG laser (yttrium aluminium garnet crystal doped with triply ionised neodymium) with a length wave for the incident laser at 1,064 nm (9,398.5 cm^{-1}). The maximum of laser power is 1.5 W. The measurement accessory is pre-aligned, only the Z-axis of the scattered light is adjusted to set the sample in the appropriate position regarding the local point. The RAM II spectrometer is equipped with a liquid-nitrogen cooled Ge detector. FT-Raman spectra (4,000-0) cm^{-1} and FTIR spectra (4,000-600) cm^{-1} were collected with resolution of 1 cm^{-1} by co-adding 128 scans for each spectrum, and we use the sampling technique ATR (attenuated total reflection) with a diamond and with a simple reflection in conjunction with infrared spectroscopy. The OPUS 6.0 software was used for the spectral acquisition manipulation and transformation.

3. Results and Discussion

3.1 Studies of Spectra of Mixture Gelucire-Quercetin Dihydrate at Room Temperature

3.1.1By Infrared Spectroscopy as a Function of the Percentage of Quercetin in the Mixture (0%, 1%, 2%, 3%, 4%, 5%)

In this paragraph we will study the Gelucire-Quercetin dihydrate mixtures of 1% to 5%, in order to seek the influence of a small proportion (by mass) of quercetin dihydrate on the excipient Gelucire 50/13 by a vibrational study using Raman and infrared spectroscopies at room temperature (25 ℃) and Raman spectroscopy at body temperature (37 ℃).

In Figs. 1 and 2, we present the IR spectra of Gelucire-quercetin mixtures at room temperature in the spectral regions 1,800-600 cm^{-1} and 3,700-2,500 cm^{-1}. In these figures, we voluntarily put the IR spectra of Gelucire and quercetin dihydrate alone to identify potential changes to the mixture. From these figures, we see that the IR spectra of the mixture are mainly dominated by vibrational modes observed for Gelucire, and the peaks of quercetin dihydrate appear only in the spectral bands 700-600 cm^{-1} and 1,700-1,500 cm^{-1} with low intensity. So in infrared spectroscopy, we do not seem to observe vibrational changes according to the percentage by mass of quercetin dihydrate on the Gelucire 50/13.

For the assignment of Gelucire in Raman and IR one must refer to the following articles [5-7].

3.1.2 By Raman Spectroscopy according to the Percentage of Quercetin in the Mixture (0%, 1%, 2%, 3%, 4%, 5%)

In Fig. 3, we present the Raman spectra of mixtures Gelucire-quercetin dihydrate at room temperature in the spectral region 1,800-0 cm^{-1}. In these figures, we voluntarily put the Raman spectra of Gelucire and quercetin dihydrate alone to identify potential changes to the mixture. We notice many changes in the vibrational behavior in three spectral areas: 600-0, 1,200-600 and 1,800-1,200 cm^{-1}. Unlike infrared spectroscopy, peaks of quercetin appeared in a very clear way in the spectra of mixture Gelucire-quercetin. To facilitate the study, we will outline the results obtained following these three spectral regions.

In Fig. 4, we present the Raman spectra of mixtures Gelucire-quercetin dihydrate at room temperature in

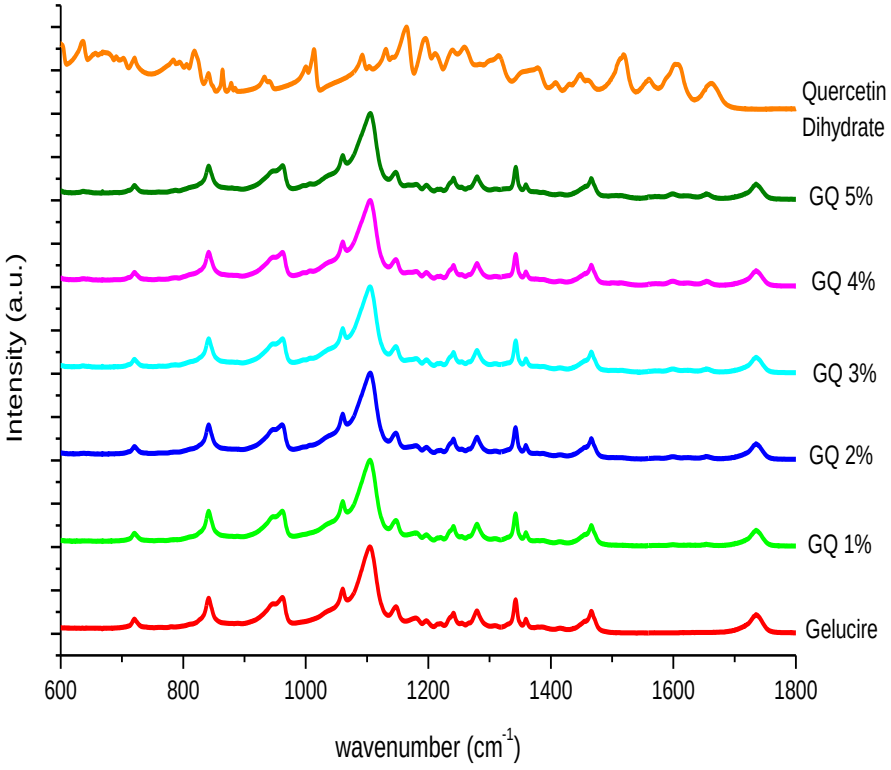

Fig. 1 IR spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 1,800-600 cm^{-1} at room temperature.

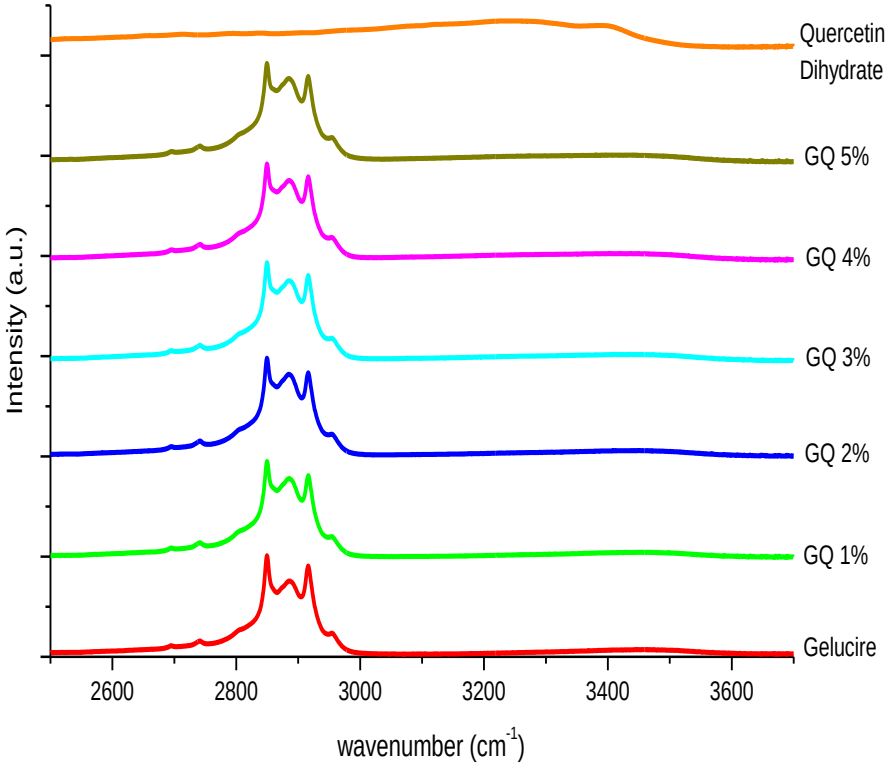

Fig. 2 IR spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 3,700-2,500 cm^{-1} at room temperature.

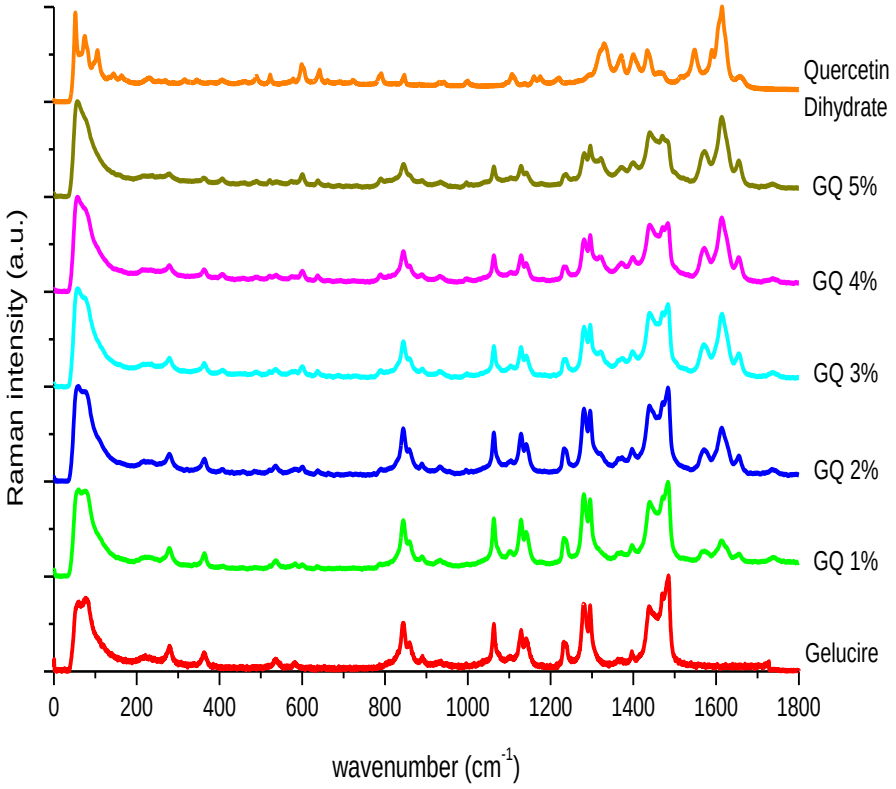

Fig. 3 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 1,800-0 cm^{-1} at room temperature.

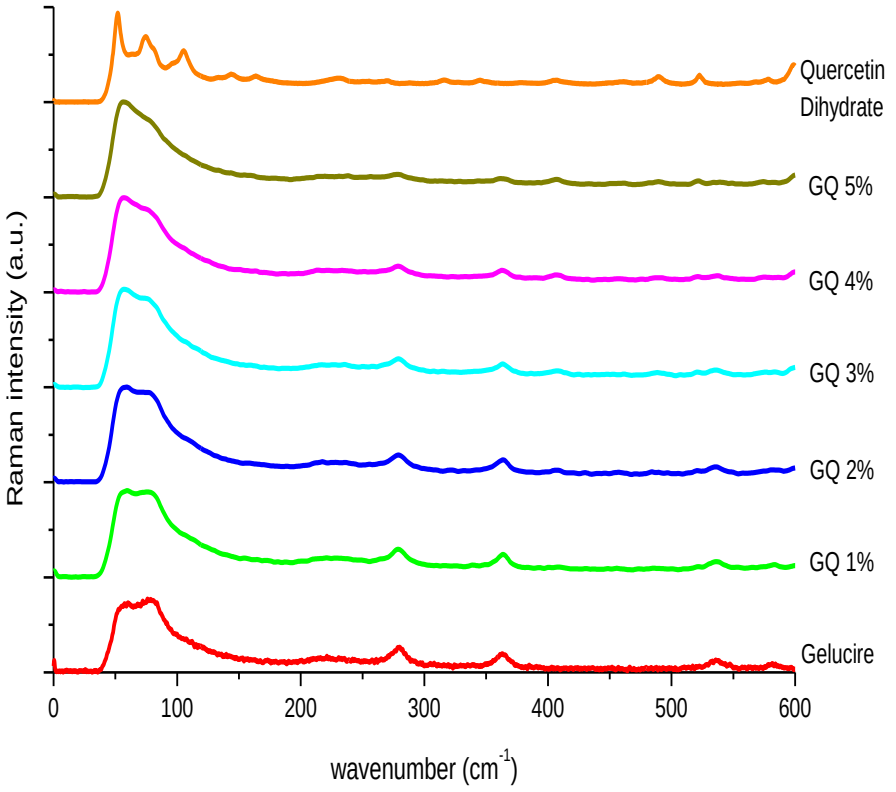

Fig. 4 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 600-0 cm^{-1} at room temperature.

the spectral region 600-0 cm^{-1}. In view of the spectra, it is noted that all the peaks of Gelucire 50/13 of this area (78, 110, 219, 280, 363, 533 and 580 cm^{-1}) have a continuous weakening in intensity as a function of the increase in percentage of quercetin dihydrate. Conversely, the peak at 59 cm^{-1} corresponding to vibrations due to intermolecular interactions presents a continuous increase in intensity between 1% and 5% quercetin.

In parallel, we find that all the peaks of quercetin dihydrate of low intensity in this spectral region have appeared from 1% of quercetin with a very low intensity, however, if the intensity ratios I_{59}/I_{75} (Fig. 5) and I_{230}/I_{280} (Fig. 6) is determined as a function of the percentage of quercetin in the mix, we note that both ratios show a continuous increase of 1% to 5% of quercetin, marking the presence of the vibrational modes of the quercetin in the mixture.

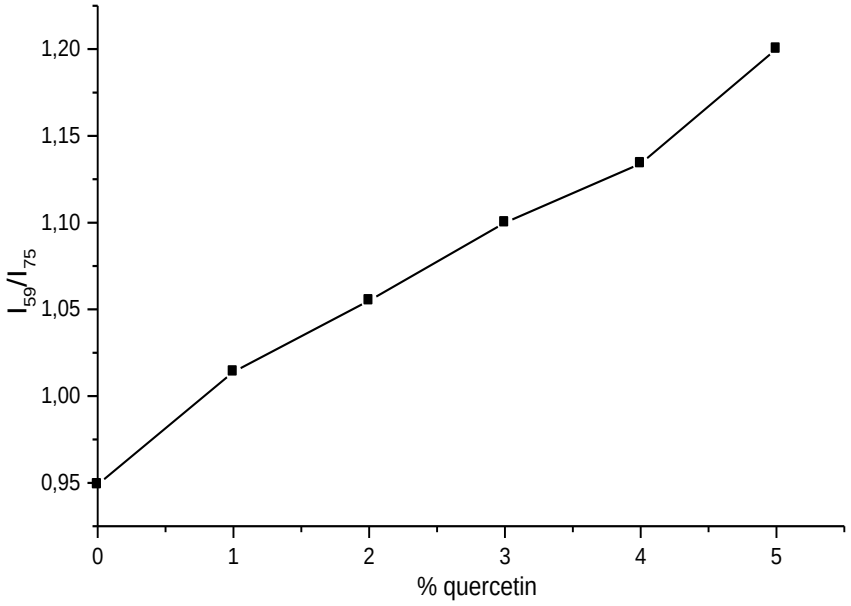

Fig. 5 Variation of the intensity ratio I_{59}/I_{75} as a function of the percentage of quercetin.

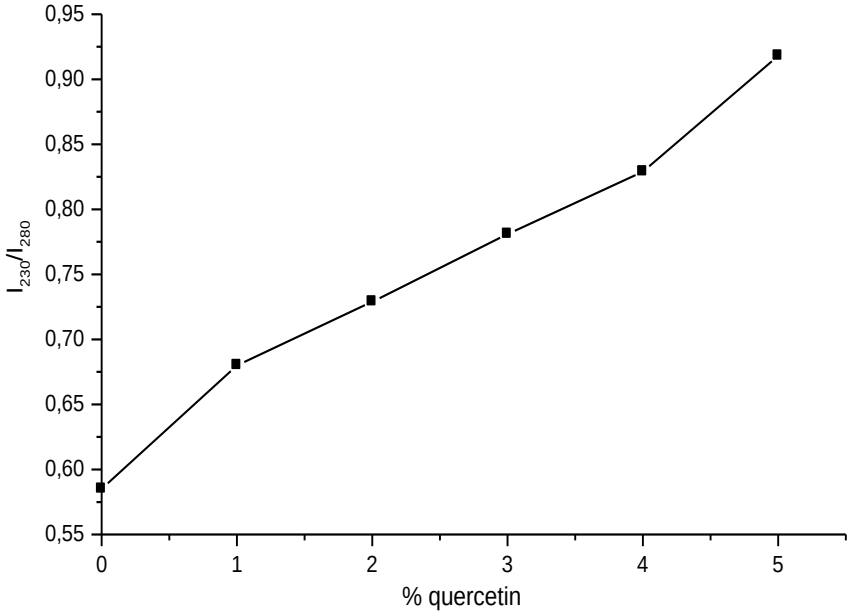

Fig. 6 Variation of the intensity ratio I_{230}/I_{280} as a function of the percentage of quercetin.

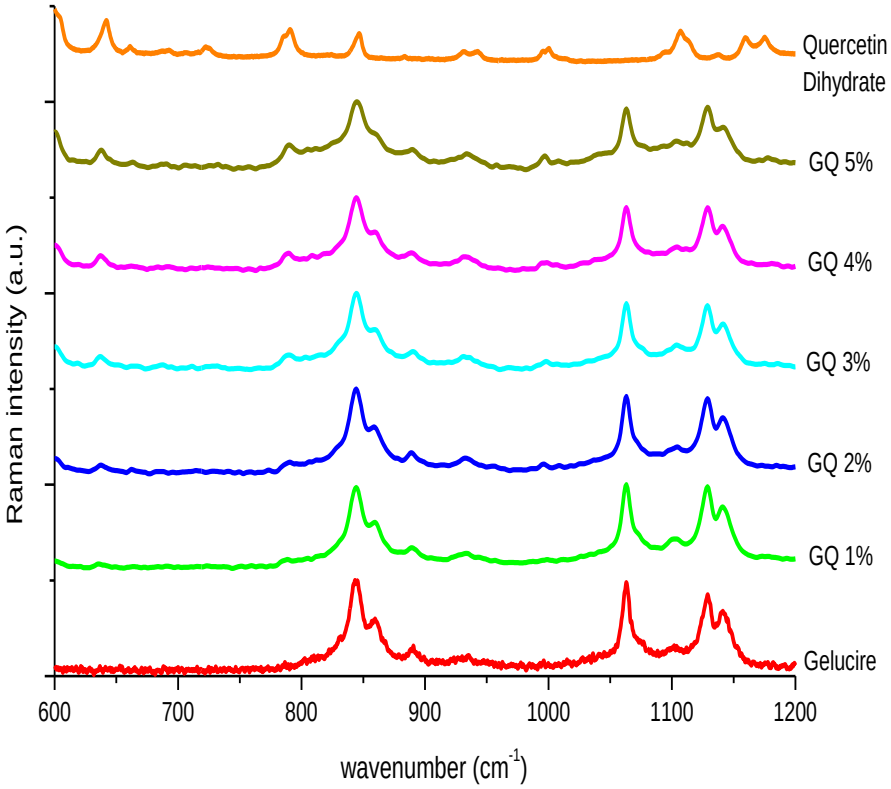

Fig. 7 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 1,200-600 cm^{-1} at room temperature.

In Fig. 7, we present the Raman spectra of mixture Gelucire-quercetin dihydrate at room temperature in the spectral region 1,200-600 cm^{-1}. As the range 600-0 cm^{-1}, this area also contains peaks which seem to vary according to the percentage of quercetin dihydrate. First, we find the peaks of Gelucire at: 843, 859, 890, 934, 1,063, 1,102, 1,128, 1,141 cm^{-1}. Note the appearance of the peaks of quercetin dihydrate (641, 790, 998, 1,106, 1,175 cm^{-1}) with low intensity from 1%. Nevertheless, we do not observe in this spectral range many changes.

In Fig. 8, we present the Raman spectra of mixture Gelucire-quercetin dihydrate at room temperature in the spectral range 1,800-1,200 cm^{-1}. In this figure, we find very clear changes compared to the spectrum of the Gelucire alone: we observe the appearance of peaks in 1,571, 1,612 and 1,655 cm^{-1} assigned to the quercetin dihydrate. We also note changes of intensities between the peaks 1,440 and 1,480 cm^{-1} in the range of $\delta(CH_2)$ and $\delta(CH_3)$. To quantify these changes, we expressed the following intensity ratios I_{1440}/I_{1480}, I_{1612}/I_{1440} and I_{1612}/I_{1480} as a function of the percentage of quercetin in the mixture shown in Fig. 9. It shows a weakening in intensity of the peak at 1,480 cm^{-1} corresponding to $\delta(CH_3)$ and a significant increase in intensity of the peak at 1,612 cm^{-1}.

For the zone 3,500-2,400 cm^{-1} (Fig. 10), we do not find the vibrational changes because the quercetin does not present significant vibrational modes in this region, and the spectra of mixture Gelucire-quercetin contain just the peaks of Gelucire 50/13.

3.2 Studies of Spectra of Mixture Gelucire-Quercetin at Body Temperature (37 ℃) by Raman Spectroscopy

In Fig. 11, we present the Raman spectra of mixture Gelucire-quercetin dihydrate at the temperature 37 ℃ in the spectral region 1,800-0 cm^{-1}. In this figure, we see the same changes that have been found in Raman spectra at room temperature (Fig. 3). By cons in the area 450-200 cm^{-1}, a broad band observed with intensity

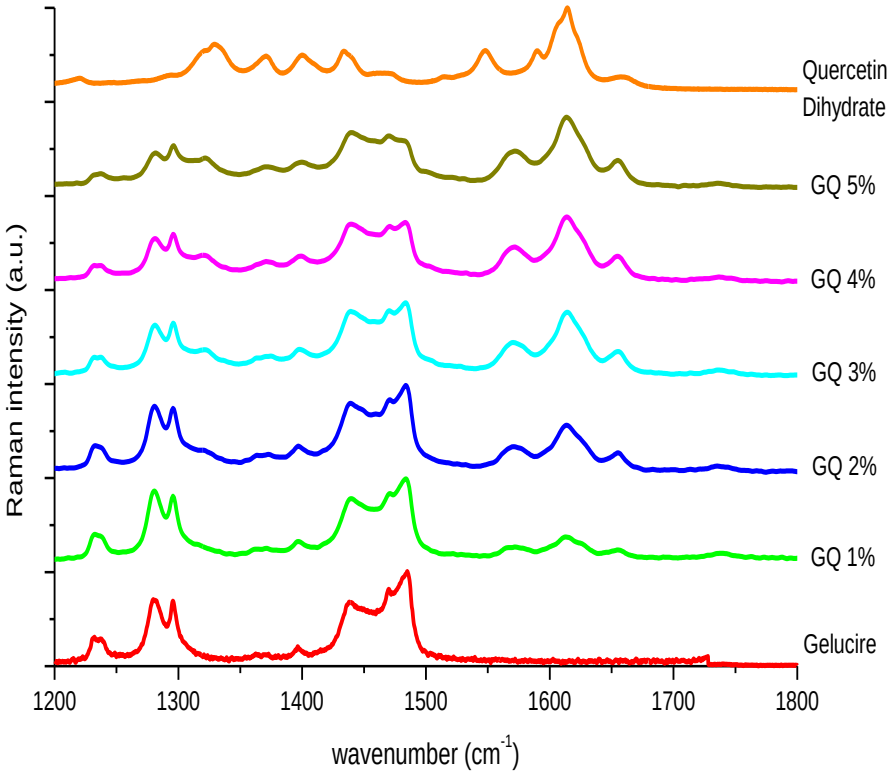

Fig. 8 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 1,800-1,200 cm^{-1} at room temperature.

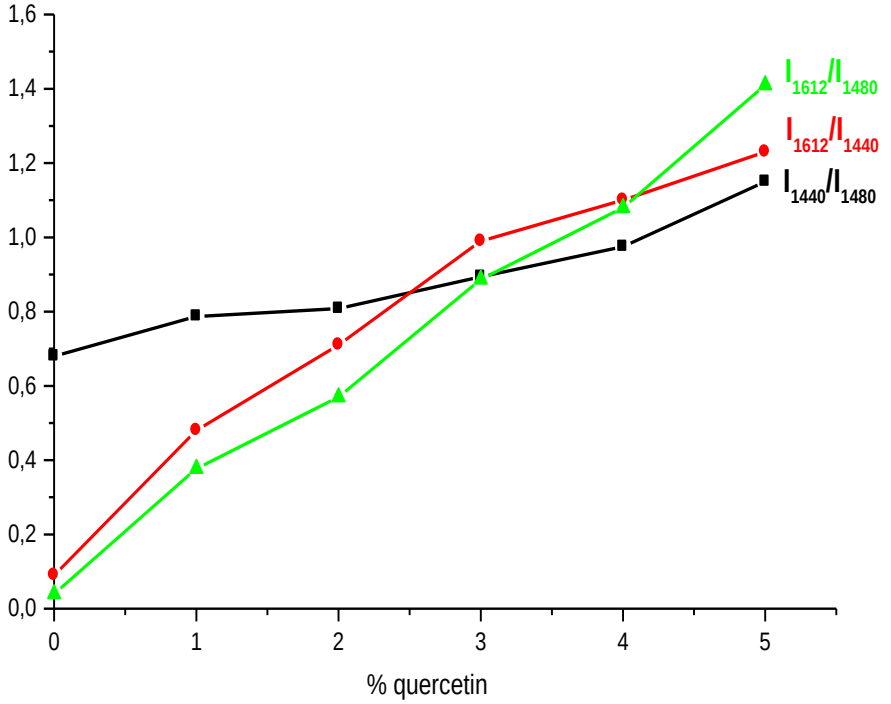

Fig. 9 Variation of the intensity ratios I_{1440}/I_{1480}, I_{1612}/I_{1440} and I_{1612}/I_{1480} as a function of the percentage of quercetin.

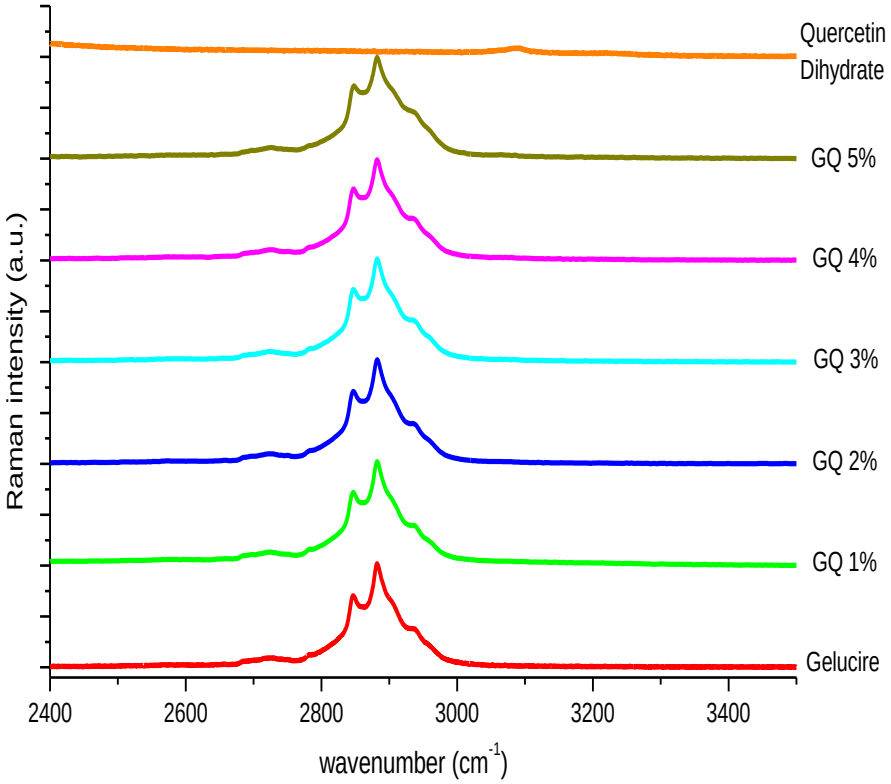

Fig. 10 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 3,500-2,400 cm^{-1} at room temperature.

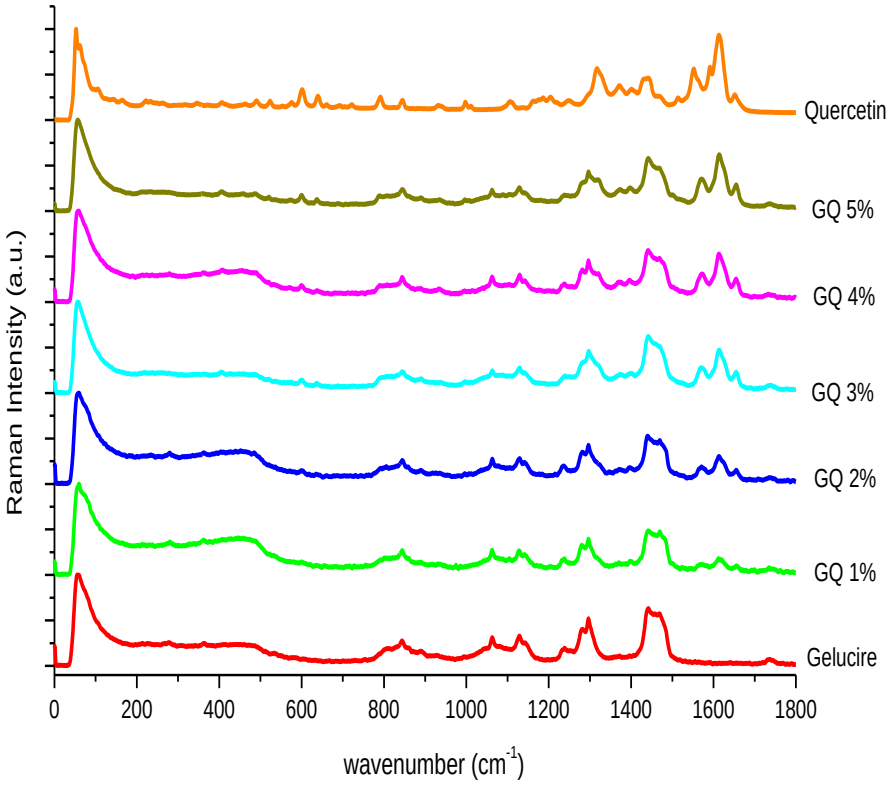

Fig. 11 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 1,800-0 cm^{-1} at the temperature 37 ℃.

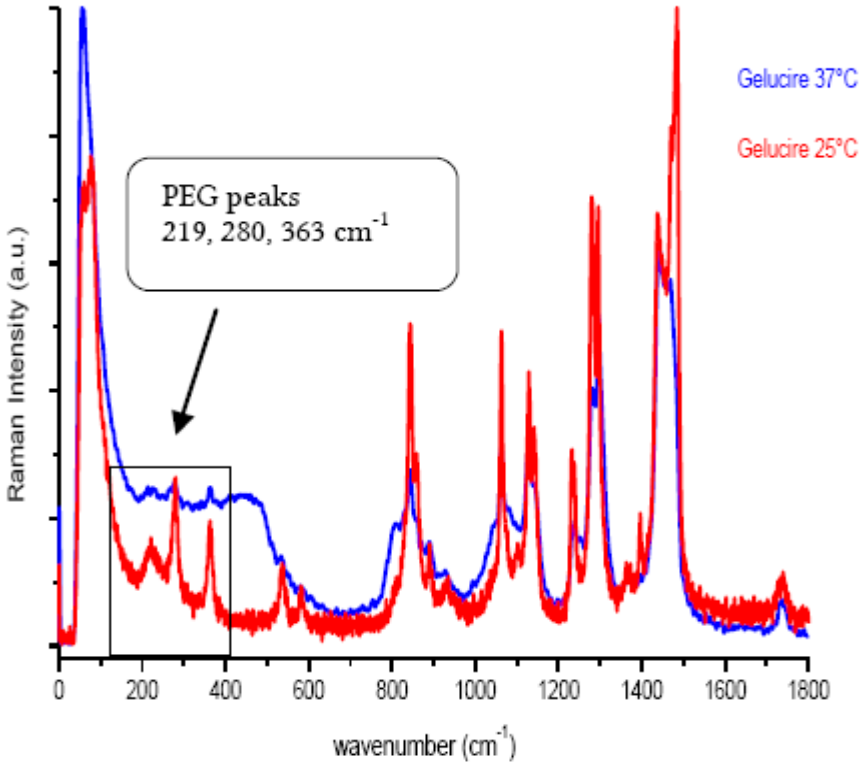

Fig. 12 Raman spectra of Gelucire 50/13 in the spectral region 1,800-0 cm^{-1} at the temperature 25 ℃ and 37 ℃.

greater than the one we had at 25 ℃. To determine whether this comes from the Gelucire or quercetin, we present the Raman spectrum of the Gelucire at 25 ℃ and 37 ℃ in Fig. 12. We observe the following changes in the region 450-25 cm^{-1}:

- The resolved doublet between 25 and 200 cm^{-1} at 25 ℃ is transformed into an unresolved doublet at 37 ℃ accordingly to the temperature rise, because these modes correspond to the intra- and inter-molecular interactions.
- There is also a peak around 500 cm^{-1} which imposes the broad band that was observed during mixing Gelucire-quercetin.

So from Fig. 12 it is clear that the changes that appeared in the area 450-200 cm^{-1} at 37 ℃ are related to Gelucire changes. Therefore it remains the determination of which components of gelucire is related to this changes.

In Fig. 13 we present the Raman spectra of PEG cast from water obtained by M. Barsbay et al. [8]. From this figure we found the same peaks appeared in the area 450-200 cm^{-1} of Gelucire-quercetin mixture at 37 ℃ and we can conclude clearly that this change is related to PEG. Brubach et al. [9] have shown that PEG 1500 formed a lamellar phase with a long spacing of 96.7 Å in a helical conformation with an orthorhombic cell under, and it existed around 32 ℃ for a semicrystalline structure which contains both crystalline and amorphous regions [9]. So when we approach to 42 ℃ the melting temperature of PEG [9] and precisely at 37 ℃ the movement of atoms increased and the structures of PEG pass to a semicrystalline structure which resulted in new interactions, deformations and rotations accompanied by intensity changes in the Raman spectrum of mixture, especially in the band 450-200 cm^{-1} where there is a hump. It appears that these changes may be related to an increase in solubility to 37 ℃.

For the zone 3,600-2,400 cm^{-1} (Fig. 14), we do not find a vibrational change, and the Raman spectra of the mixture are mainly dominated by vibrational modes observed for Gelucire 50/13.

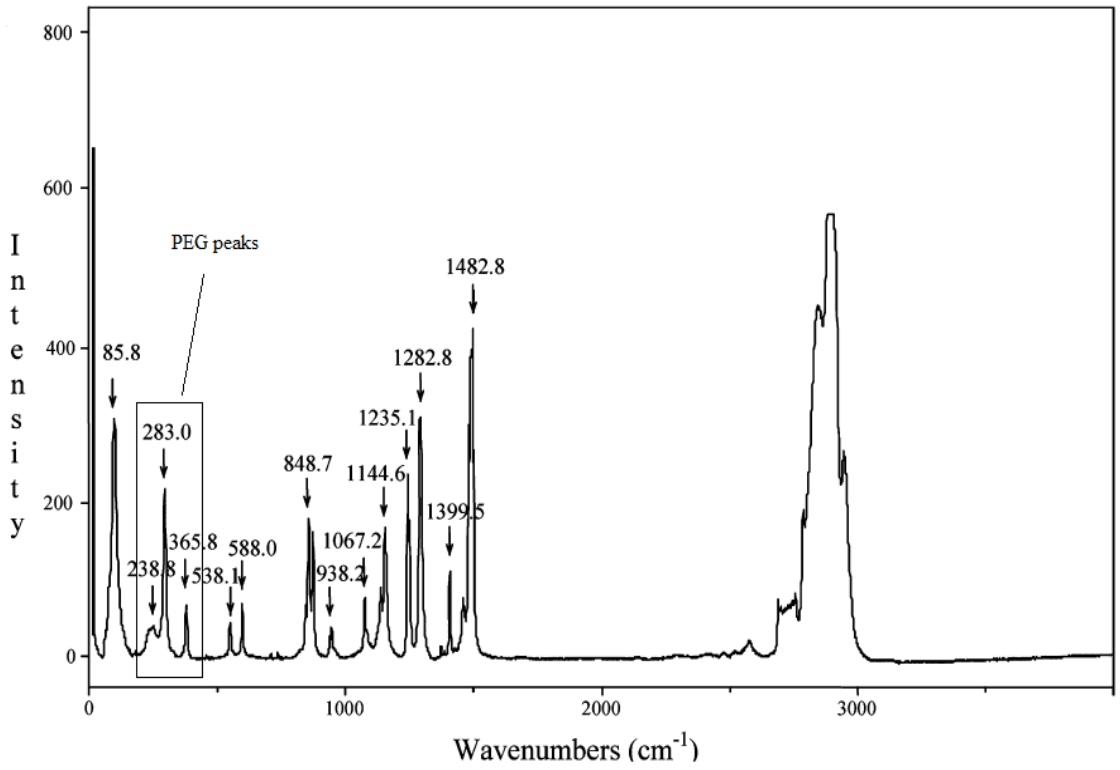

Fig. 13 Raman spectra of PEG cast from water [8].

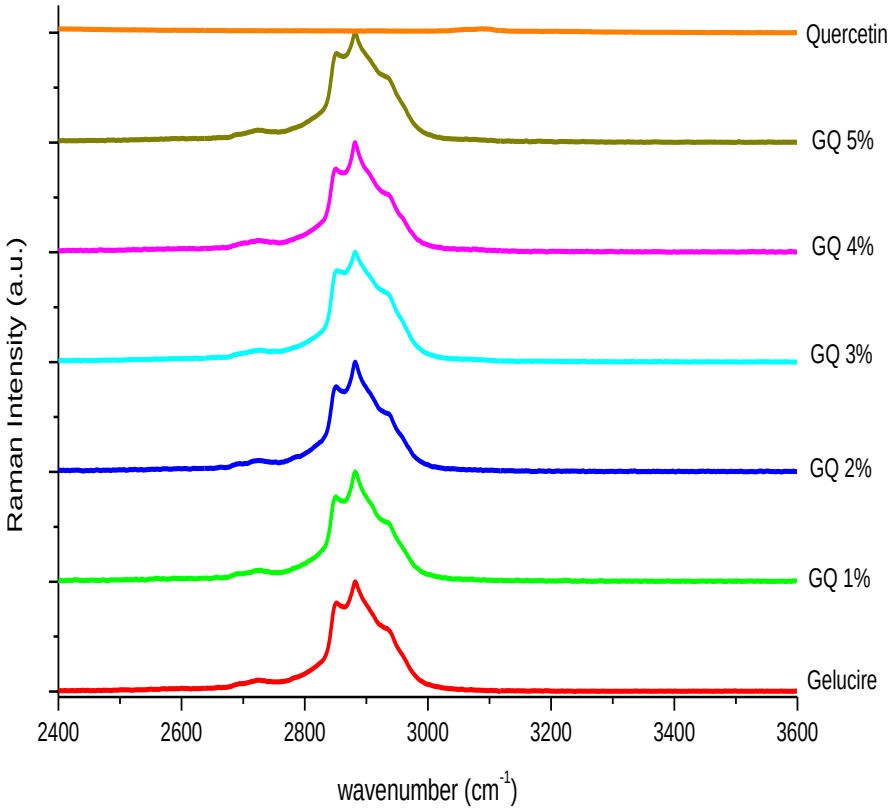

Fig. 14 Raman spectra of mixture Gelucire-quercetin (from 1% to 5%) in the spectral region 3,600-2,400 cm^{-1} at the temperature 37 ℃.

4. Conclusion

In this work, we studied the mixture Gelucire-quercetin dihydrate (from 1% to 5%) at room temperature and body temperature by Raman and IR spectroscopies. We observed that the Raman spectra of mixture unlike infrared spectroscopy, present a mix of peaks between the Gelucire and quercetin dihydrate. The appearance or the disappearance or frequency shift of some peaks in Gelucire-quercetin spectra seems that the gelucire creates new bonds and interacts with the molecules of quercetin which seems to prove that the mixture Gelucire-quercetin improves the solubility of quercetin. At a temperature of 37 ℃, little vibrational changes were observed, only changes in the Gelucire in the spectral region 500-0 cm^{-1} were detected which are related to PEG which is very sensitive to the change in temperature and hydration.

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