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SHORT COMMUNICATION article

Determination of the structural parameters of Repaglinide in tablet: an antidiabetic drug, using Spectroscopic methods

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Abstract: The spectroscopy area provides molecular-level information about an anti-diabetic drug through qualitative and quantitative analysis, Repaglinide is an antidiabetic medication in the meglitinide class that is used to treat type II diabetes mellitus. The objective of this work was to characterize Repaglinide by using UV spectroscopy (UV), nuclear magnetic resonance (NMR), and infrared spectrometry (FTIR). The UV results showed that the maximum absorption was at 208, 243, and 285 nm. The IR spectra obtained are consistent with those described in the literature. The NMR-1H spectra revealed information about the various hydrogen and carbon atoms in the molecule as well as their chemical surroundings. The provided methods were successfully employed to control a drug with great accuracy and precision.

Introduction

Type 2 diabetes is a fairly prevalent progressive illness. It is a chronic metabolic disorder in which the body becomes resistant to the effects of insulin [1-3]. Meglitinides are insulin secretagogues, which stimulate the pancreas to secret insulin [4]. Repaglinide, a Meglitinide derivative, is the first oral drug used to treat type 2 diabetes [5-7]. Repaglinide lowers blood glucose by stimulating the pancreas to generate insulin. Sulfonylureas accomplish this by inhibiting ATP-dependent potassium channels in the membranes of beta cells [8, 9]. The structure name of Repaglinide is S (+) 2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl) phenyl) butyl) amino)-2-oxoethyl) benzoic acid (**Figure 1**) [10-12].

Several synthetic medications have been developed due to advancements in science and technology. The growing use of these anti-diabetic medications necessitates the creation of fresh and innovative techniques for accurately identifying these medications in pharmaceutical forms and biological fluids [2]. A comprehensive literature search reveals that past studies have reported the investigation of molecular structure by several spectroscopic analytical methods. Among these methods are Infrared Spectroscopy (FT-IR) [12-15], UV spectrophotometric [9, 13], and Nuclear Magnetic Resonance (NMR-1H) [3, 16]. Ultraviolet-visible (UV-Vis) spectroscopy is a common analytical technique for determining a sample's absorption of ultraviolet and visible light. The foundation of this spectroscopic technique is the idea that molecules absorb light at particular wavelengths, which can provide important details about the electronic structure and characteristics of the sample. The primary purpose of FTIR spectroscopy in Repaglinide is to provide information regarding

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functional group type analysis. Nuclear magnetic resonance (NMR) is a specialized description technique that we use to determine the Repaglinide chemical composition and its structural characteristics. Furthermore, NMR-1H spectroscopy provided precise information on proton environments, which confirmed the presence of diastereoisotopic configurations [4, 10, 17]. In this regard, spectroscopic characterizations of the Repaglinide molecule, which is the active element of an antidiabetic medicine usually given as Diaglinide or Novonorm, were carried out utilizing FT-IR, NMR-1H chemical, and UV spectrophotometric analysis methods.

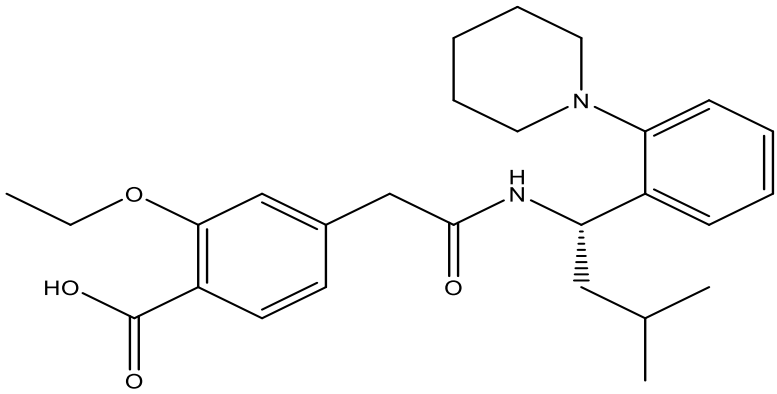

Figure 1: Chemical structure of Repaglinide

Materials and methods

Novo Norm® tablets (Batch Nos. 2077884), each tablet containing 2.0 mg Repaglinide (Novo Nordisk, Bagsvaerd, Denmark), Were purchased from a local market in Algeria. Methanol was purchased from Riedel-deHaën (Sleaze, Germany). FT-IR spectrum of the Repaglinide molecule in the region 400-4000 cm^{-1} using the potassium bromide (KBr) pellet technique at room temperature, was recorded with Fourier-transform infrared spectrometer "Cary 630 FTIR" in the solid phase of the sample. The UV-visible spectrometer (Specorde 50 plus) was used to obtain the absorption spectra of the title molecule in the region 200-400 nm. The sample solution of Repaglinide (2.0 mg) was prepared by dissolving 0.05 mg of Repaglinide in methanol. The NMR-1H (proton nuclear magnetic resonance) prediction of Repaglinide using MestreNova Software provides information about the proton environment in the molecule, in particular information about its diastereoisomeric. To process NMR-1H data, we import NMR-1H data into MestReNova software, select the desired NMR-1H data file, adjust the phase and baseline correction, use the integration tool, adjust peak picking parameters, analyze multiplet patterns, assign peaks to specific protons, generate processed data reports, and save the data in MestReNova format.

Results and discussion

Vis-UV spectroscopy analysis: The Vis- UV absorbance spectra of Repaglinide in methanol present three characteristic bonds of absorption (**Figure 2, Table 1)**.

Table 1: Result of VIS-UV spectroscopic analysis of Repaglinide

	Bonde I	Bonde II	Bande III
λ_{max}	208	243	285
ΔE kcal/mol	137.579	117.763	100.408

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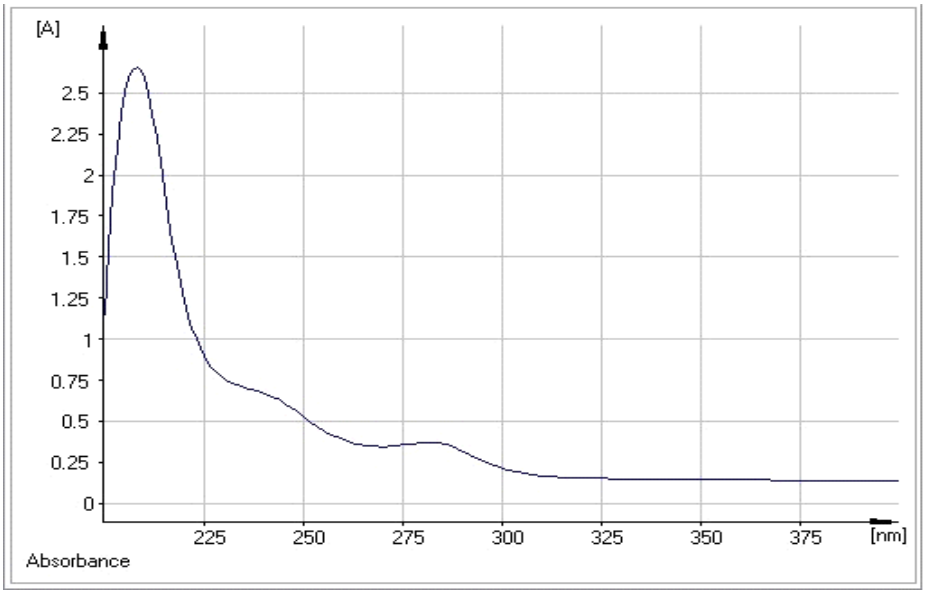

Figure 2: Vis- UV absorbance spectra of Repaglinide

The first band situated at λ_{max}=208 nm with an energy of about ΔE=137.579 kcal/mol attributed to electronic transition π→π* due to the presence of double bonds C=C conjugates in the aromatic ring of the molecule. The second band situated at λmax=243 nm with an energy of about ΔE=117.763Kcal/mol attributed to electronic transition π→π* which corresponds to the double bonds of (C=O acid and C=N amide). The third band situated at λ_{max}=285 nm with an energy of about ΔE=100.408 Kcal/mol attributed to electronic transition n→ π which corresponds to the free doublet of heteroatoms of azote and oxygen.

Table 1 and Figure 3 show that the electronic transition energy is inversely proportional to the wavelength, which means that as the transition energy lowers, the wavelength increases. This finding gives information on the stability of the molecule based on the number of existing intramolecular interactions (electronic and structural).

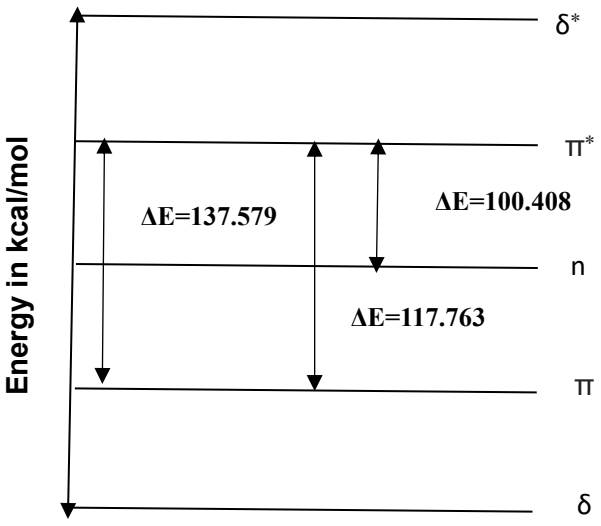

Figure 3: Energy diagram of Repaglinide

Vibrational spectroscopy IR: The infrared spectrum of Repaglinide presents 26 characteristic absorption bands (**Figure 4**) and the results of analysis by IR spectroscopy of Repaglinide are summarized in **Table 2**.

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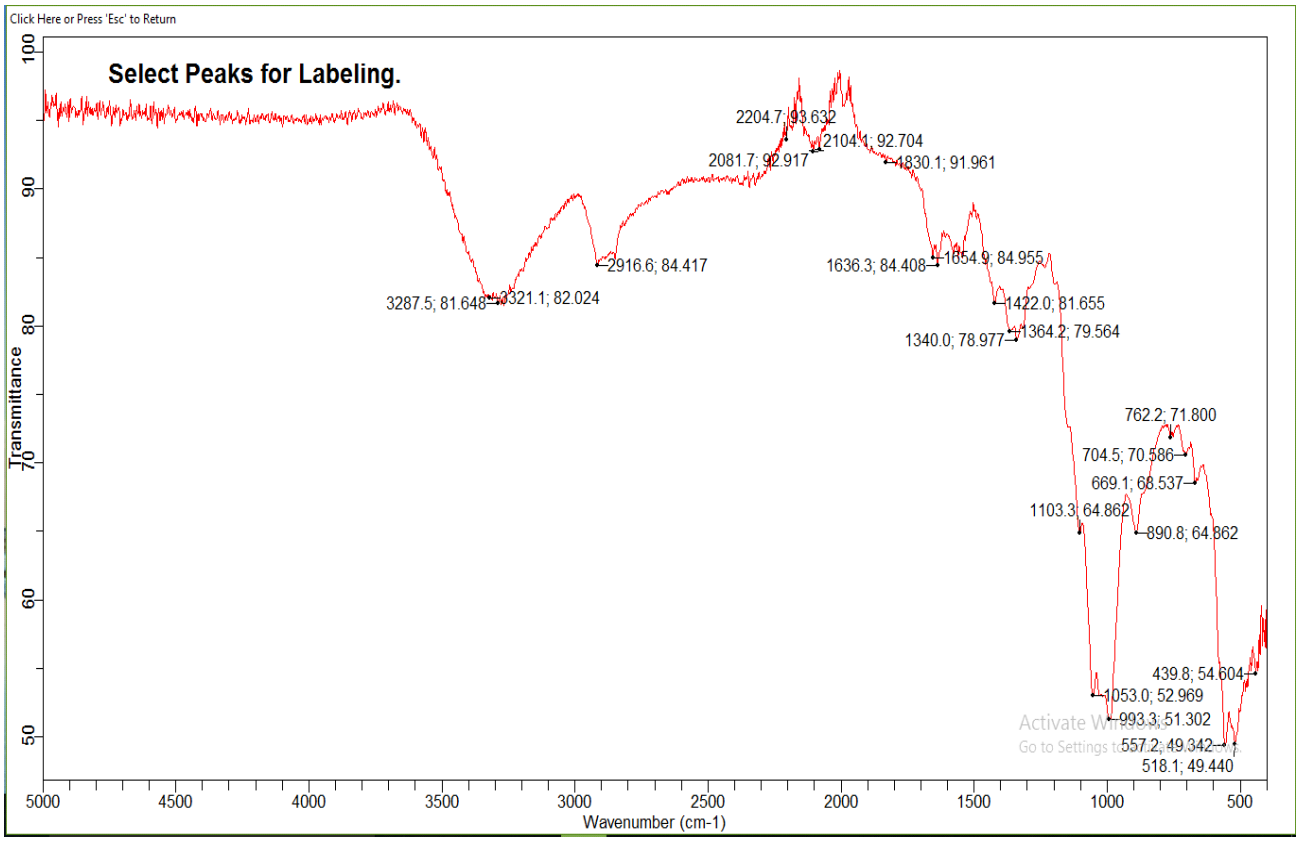

Figure 4: The infrared spectrum (IR) of Repaglinide

Table 2: The groups that belong to each frequency are shown in the specter of the FTIR study

	ν (cm^{-1})	δ (cm^{-1})	γ (cm^{-1})
CH_2, CH_3	2800-2850-2916	1340-1364	704-762
C=C aromatic	1422-1510-1550		
C-H aromatic	3320-3000		620-669
C=O acid	1720		
C-O acid	1103-1130		
O-H acid	2770- 2660		
C=O amide	1830		
N-H amide	3287	1560-1636	
C-O ether	1053-1180-1210-1280		

The first three characteristic bands of transmittance fine located respectively at 2800, 2850, and 2916 cm^{-1} correspond to the valence vibration symmetric and asymmetric of the links between C-H of CH_3 and CH_2. This is confirmed by the existence of two characteristic bands fine located at 1340, 1450 cm^{-1} corresponding to the deformation vibration in the same plan symmetric and asymmetric of the links between C-H of CH_3 and CH_2 and also by two fine characteristics bands located at 704, 762 cm^{-1} correspond to the deformation vibration out of the plane of the C-H bonds of CH_2.

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The aromaticity of the molecule is validated by the presence of three characteristic bands transmittance fine matched towards 1422, 1510, and 1550 cm^{-1} corresponding to the valence vibration of the connection between C=C. It is confirmed by the presence of two fine bands towards 3000, 3320 cm^{-1} corresponding to the valence vibration of aromatic C-H bands, and two fine characteristic bands located at 620, 669 cm^{-1} correspond to the deformation vibration out of the plane of the aromatic C-H bands.

Four characteristic bands of transmittance fine located at 1053, 1180, 1210, and 1280 cm^{-1} correspond to the valence vibration of the links C-O of ether. The acid function is characterized by the presence of an absorption band around 1720 cm^{-1} corresponding to the valence vibration of the C=O carbonyl function and the presence of two bands located at 1103, 1130 cm^{-1} corresponds to the deformation vibration of the links between C-O also by the presence of two fine absorption bands located at 2770, 2660 cm^{-1} attributed to the valence vibration of the links O-H of acid. Another characteristic band of absorption located at 1830 cm^{-1} is attributed to the valence vibration of the connection between C=O of amide. A band intense matched towards 3287 cm^{-1} corresponds to the valence vibration of the intramolecular hydrogen links N…H and two characteristic bands of absorption located 1560,1636 cm^{-1} correspond to the deformation vibration in the same plan of the links of amide.

NMR-1H spectroscopic analysis: The determinations of the structure of Repaglinide, based on the NMR-1H spectra indicate the presence of 19 signals. The NMR-1H spectrum analysis of Repaglinide shows the presence of singular two protons at 3.75 ppm (S, 2H). The signals at 1.26, 1.40, 1.60, 1.64, 3.24, 3.49, and 7.16 ppm attributable respectively to (H20, H9, H31-H33, H32, H29a,b, H30a,b, H23).Three signals a proton resonating at 6.17, 6.80, and 7.11 ppm attributable respectively to (H24, H26, H25). Four signals at 7.32, 8.15, and 9.73 ppm are attributable respectively to (H4, H3, H15). The signals resonating at 5.06, 4.05, 1, and 1 ppm are attributable to (H16, H8, H21, H22) (q, 2H; d, 3H; d, 3H) respectively presence of methyl. Two multiply signals (H19a, H19b) (t, 1H) resonant at 1.46 ppm presence of diastereoisomeric protons (**Figure 5, Table 3**).

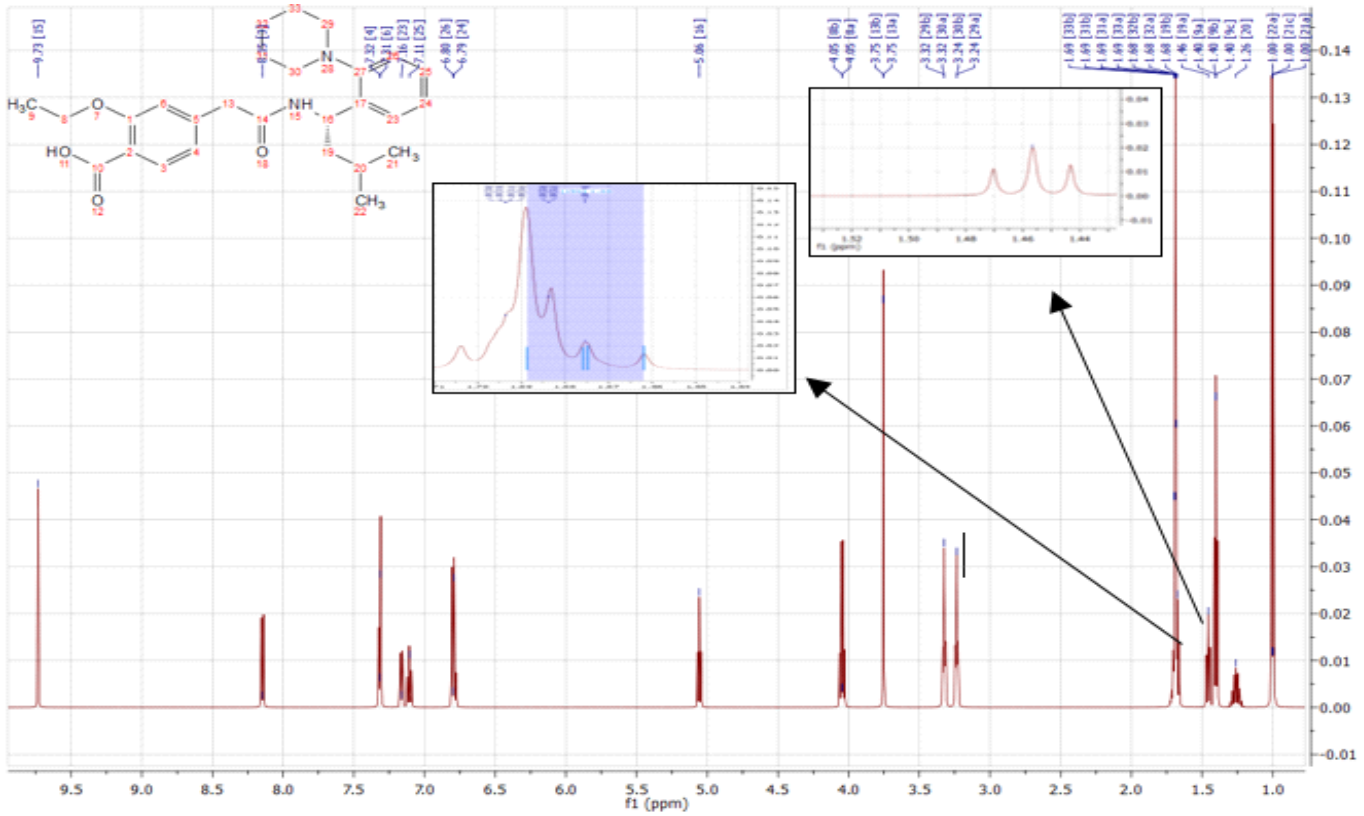

Figure 5: NMR-1H spectrum of Repaglinide using Mestre Nova Software

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Table 3: Chemical shifts in NMR-1H and the attribution of Repaglinide signals

Position	NMR-1H
3	8,15 (d, 1H)
4	7,32 (d, 1H)
8	4,05(q, 2H)
9	1,40 (t, 3H)
13	3,75 (S, 2H)
15	9,73 (d, 1H)
16	5,06 (d, 1H)
19 a,b	1,46 (dd, 1H)
20	1,26 (d sept, 1H)
21, 22	1 (d, 3H)
23	7,16 (d, 3H)
25	7,11 (D, 1H)
26	6,80 (D, 1H)
29 a,b	3,24 (dd, 2H)
30 a,b	3,49 (DT, 2H)
31, 33	1,60 (DT, 2H)
32	1,64 (DTT, 2H)

Conclusion: Spectroscopic approaches such as UV, IR, and NMR-1H were used to investigate Repaglinide, yielding valuable information on its chemical structure and properties. The UV spectra show that the molecule has the greatest absorption at 208, 243, and 285 nm. Characteristic functional groups including carbonyl, amide, and aromatic groups have been observed in the IR spectra. The NMR-1H spectra provided information about each of the hydrogen atoms in the molecule, as well as their chemical environments. Overall, the use of multiple spectroscopic methods allowed for a full analysis of Repaglinide, which is important for understanding its pharmacological and therapeutic effects.

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Author contribution: NB conceived and designed the study and DH collected the data. DH, KS & MB contributed in data analysis. DH & NB performed and interpretated data analysis. Dh & NB drafted and revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
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Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.