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FOURIER TRANSFORM INFRARED SPECTROSCOPY FOR QUANTITATIVE DETERMINATION OF VALSARTAN IN BULK MATERIALS AND IN PHARMACEUTICAL DOSAGE FORMS

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The present paper illustrates the potential applications of Fourier Transform Infrared Spectroscopy (FT-IR) in pharmaceutical analysis. A simple, rapid, non-destructive and green (FT-IR) spectroscopy method for quality control evaluation of valsartan was developed, using potassium bromide (KBr) as a matrix to quantify the drug in bulk pharmaceutical materials and in pharmaceutical dosage forms. The sample preparation was avoided except grinding for disk composition and excluded the use of organic solvents. Absorbance obtained for the carbonyl band (C=O) located at 1732 cm-1 was used for the development of calibration curve based on simple Beer-lambert's law. Method validation was performed according to the International Conference on Harmonization (ICH) guidelines. Linearity, accuracy, precision, robustness and selectivity were evaluated and showed acceptable results for method validation in the concentration range of (0.5 - 2.5% w/w). The developed and validated method was suitable for the quality control analysis of valsartan in bulk materials and in pharmaceutical dosage forms.

Keywords: *FT-IR; Quantitative; Absorbance.*

INTRODUCTION

Valsartan, chemically (2*S*)-3-methyl-2-[pentanoyl-[[4-[2-(2*H*-tetrazol-5-yl) phenyl] phenyl] methyl] amino] butanoic acid (Figure 1) is an angiotensin II receptor blocker (ARBs) that treats high blood pressure and heart failure[1]. Valsartan physiological effects lead to reduced blood pressure, reduced cardiac activity, lower aldosterone levels, and increased excretion of sodium[1]. According to the review published by Satriani et al., a variety analytical methods have been proposed to quantify valsartan (alone or in mixtures with other drugs) in bulk materials, in pharmaceutical dosage forms and biological fluids[2]. Various methods including HPLC[3&4], HPTLC[5], RP-HPLC[6&7], UV spectrophotometry[8&9], spectrofluorimetry[10] and voltammetry[11] have been reported for the estimation of valsartan. However, until now, no Fourier transform infrared (FT-IR) spectroscopy has been reported for the quantitative determination of valsartan in bulk materials and in pharmaceutical dosage forms.

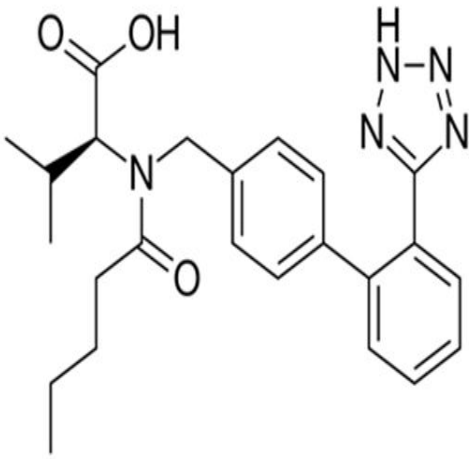

Fig. 1: Valsartan structure.

Fourier transform infrared spectroscopy (FT-IR) is an analytical technique based on the

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capability of vibration of a molecule. The infrared spectrum is section of the electromagnetic spectrum[12]. FT-IR spectroscopy can be used widely in the pharmaceutical and drug laboratories for the identification of compounds[13], structural investigations[14], impurities[15&16], polymorphism[17] and for monitoring dissolution of pharmaceutical dosage forms[18]. In addition to the aforementioned uses of this technique in qualitative analysis, FT-IR spectroscopy is used for quantitative purposes due to its simplicity and availability in most pharmaceutical laboratories[12]. Since the wavenumber and its particular intensity of absorption depend on a specific group in the chemical structure of a substance, it is potential to perform quantitative analysis based on peak heights or ideally by methods depending on integrated intensities[19]. Furthermore, it is often possible to select an absorption band for each compound of a combination without interference between them[20].

Several pharmaceutical substances have been quantitatively analyzed. The literature reveals FT-IR method for the quantification of Roxithromycin[21], Ampicillin sodium[22], Paracetamol[23], Doxycycline[24], Amoxicillin[25], and simultaneous determination of Paracetamol, Caffeine and Acetosal contents in a combination tablet dosage form[26].

Therefore, the major objective of the present study was to develop a simple, rapid and cost effective method for the quantification of valsartan, either alone or in combination, in solid-state samples and explore the use of FT-IR spectroscopy in pharmaceutical analysis. The proposed FT-IR spectroscopy method was performed on standard valsartan and two marketed solid dosage forms (Label claim 160mg valsartan).

MATERIALS AND METHODS

Equipment and software

The FT-IR analysis was carried out on ALPHA-T spectrophotometer (Bruker, Germany). FT-IR spectrum was recorded in the Mid-range between 4000 and 400 cm^{-1} using 16 scans for every sample with a nominal resolution of 4 cm^{-1}.

Version 6.5 of OPUS software developed by Bruker was employed for spectrum measurements. Generated spectrums were automatically corrected by air background spectrum which were previously measured. All results were computed taking into account both, peak area and peak height, after an adequate baseline correction. The development of calibration curves was performed utilizing Microsoft Excel. (2016).

The other equipment used are as follows: Agate mortar and pestle, analytical balance ±0.1 mg (Sartorius, Germany),13mm evacuable disk dies (Specac, United Kingdom) and hydraulic press (Specac, United Kingdom) were used for the preparation of disks as well as an oven (Memmert, Germany).

Chemicals and reagents

Working standard sample of valsartan was obtained as a gift from Ibn-Alhaytham pharmaceutical Industries (Aleppo, Syria). Commercial pharmaceutical 160mg/capsule Valsartan (Lot. 053, Mfg. 05/2018, Exp. 05/2022) was purchased from local pharmacy (Aleppo, Syria)), manufactured by Ibn-Alhaytham pharmaceutical Industries (Aleppo, Syria). Other solid pharmaceutical dosage form which is tablets containing valsartan in binary mixture was used. Commercial pharmaceutical 160 - 5 mg/tablet valsartan - amlodipine (Lot. 021, Mfg. 04/2019, Exp. 04/2023) was purchased from local pharmacy (Aleppo, Syria), manufactured by Unipharma pharmaceutical industries (Damascus, Syria)). Excipients present in the pharmaceutical dosage forms are sodium lauryl sulfate, microcrystalline cellulose, crospovidone and magnesium stearate. Potassium bromide (KBr) was also used as a diluent (SURCHEM, United Kingdom).

Preparation method

In general, Samples prepared as a solid disk, dilution with dry potassium bromide (KBr) followed by compression in a hydraulic press[20]. The disk method can be efficiently applied for quantitative analysis since the concentration of the sample and the thickness of the disk can be controlled[27].

Stock and working standard mixture preparation

Stock standard mixture containing valsartan at a concentration of 1:10 was prepared by accurately weighing 80mg of valsartan working standard sample and 720 mg of Potassium bromide (KBr). The diluent was

KBr dried at 105°C in an oven to achieve a constant weight[27]. This dilution was performed to facilitate and reduce the possible errors in weighing. Working standard mixtures were prepared immediately before use by suitable dilutions of the corresponding stock mixture to appropriate concentration levels by using KBr as a diluent at a concentration of 1:100. For example, to prepare a disk at (2%w/w) concentration, amount of stock mixture equivalent to 2 mg of valsartan were taken and homogenized with 130 mg of KBr, making the total disk weight of 150 mg. Mixing could be effected by grinding in a smooth agate mortar[27]. The mixture was then placed in a 13 mm evacuable disk die and a pressure of 10 tons was applied 10 min by hydraulic press to obtain a transparent disk.

Preparation of sample disks

The average weight of the content of twenty capsules (containing valsartan as a sole active ingredient) was determined. Thereafter, an amount of this powder, which was proportionate to the labeled content of one capsule, was mixed and ground with KBr to obtain the stock mixture (1:10). To give final concentration of (2% w/w), a suitable dilution with KBr was made. The mixture was then placed in a 13 mm evacuable disk die and a pressure of 10 tons was applied 10 minutes by hydraulic press to obtain a transparent disk.

To determine valsartan in combination (binary mixture), twenty tablets of commercial samples were crushed and powdered. After that, an amount of these powders, which it was equivalent to the labeled content of one tablet, was mixed and ground with KBr to obtain the stock mixture (1:10). To give final concentration of (2% w/w), a suitable dilution with KBr was made. The mixture was then placed in a 13 mm evacuable disk die and a pressure of 10 tons was applied 10 minutes by hydraulic press to obtain a transparent disk.

Preparation of excipients present in solid pharmaceutical dosage forms of valsartan disks Four independent disks were prepared, containing each excipient present in the solid pharmaceutical dosage form including Sodium lauryl sulfate, magnesium stearate, microcrystalline cellulose and crospovidone.

RESULTS AND DISCUSSION

Results

Selection of the analytical band

In order to identify the possible band to be used in the development of the method, the spectrum of pure Valsartan was first obtained using FT-IR spectroscopy. As shown in (Figure 2) several characteristic bands of valsartan could be observed in the spectrum. The main bands identified were: a broad band related to the N-H functional group which was located at 3420 cm^{-1}, bands related to the axial stretching of C-H of the methyl groups which were located at 2963 cm^{-1}, 2933 cm^{-1} and 2873 cm^{-1}, the sharp and intense peak found at 1732 cm^{-1} which could be assigned to the stretching of the C=O group present in the carboxylate functional group, the characteristic peak at 1603 cm^{-1} related to the stretching of a C=O present in the amide functional group and another band at 1513 cm^{-1}showing an N=N bond. Other important bands present in the spectrum were those observed in the range of 1205 - 1025 cm^{-1} which appeared due to the absorption associated to the tetrazole ($–CN_4$) ring and the complex region of 900–600 cm^{-1} indicating skeletal vibration and an aromatic ring in the valsartan structure[28-30].

Second, four independent disks were prepared, containing each excipient present in the pharmaceutical dosage form including sodium lauryl sulfate, microcrystalline cellulose, crospovidone and magnesium stearate (Figure 3). Subsequently, a comparison was performed between the spectrum of pure Valsartan and that of each excipient present in solid pharmaceutical dosage forms in order to determine the suitable isolated peak for the quantitative analysis. As shown in (Figure 4), there was no overlap with the peaks of the excipients and pure valsartan at the chosen peak 1732 cm^{-1}, which corresponds to a particular band of the valsartan structure (carbonyl group), and its absorbance was quantitatively analyzed (Figure 5).

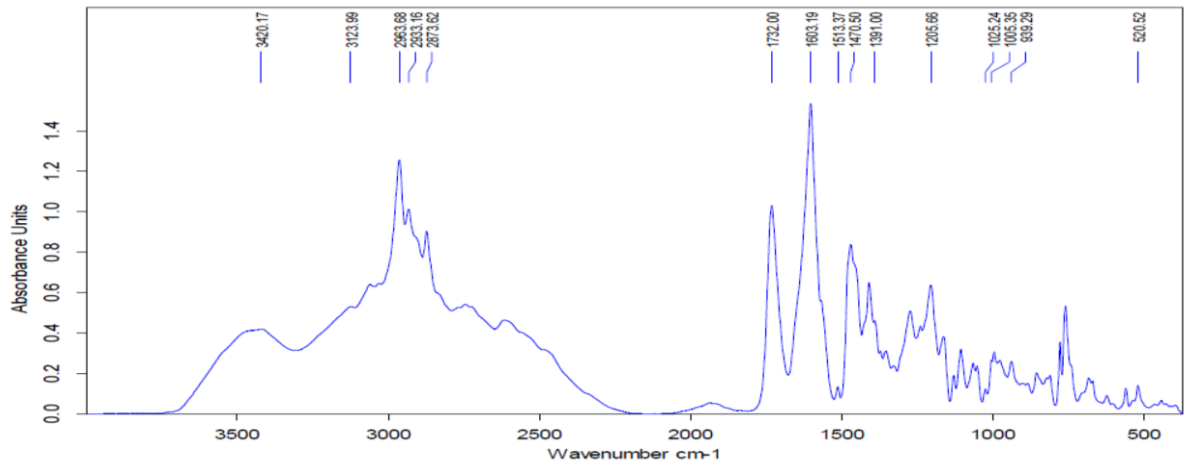

Fig. 2: FT-IR spectrum of pure valsartan in the whole mid-infrared region.

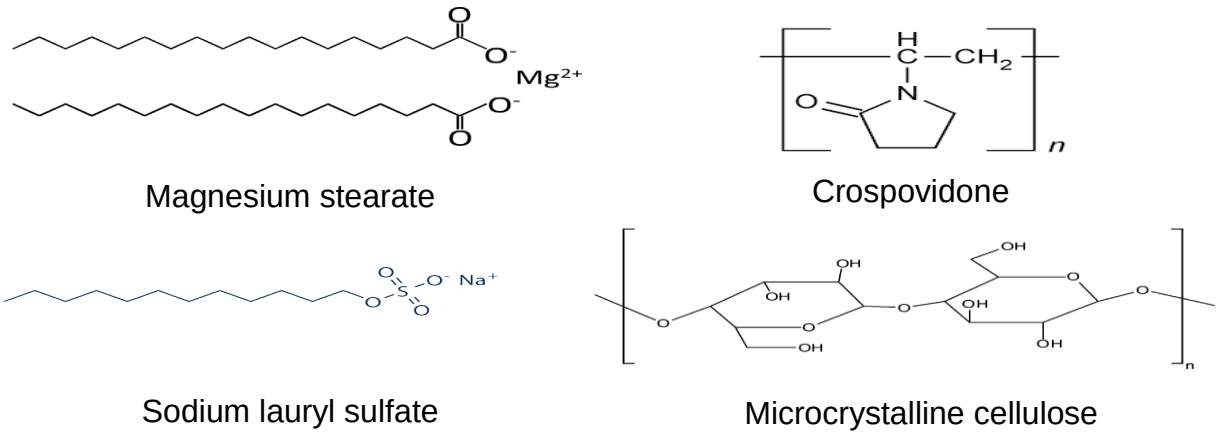

Fig. 3: Chemical structure of excipients.

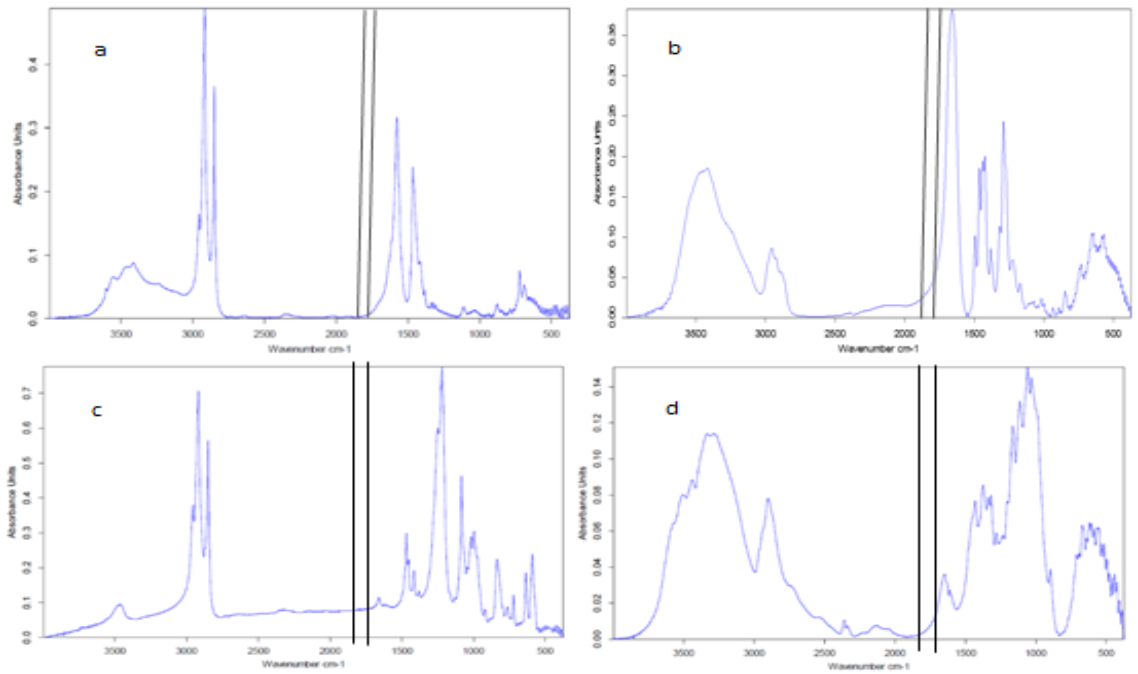

Fig. 4: FT-IR spectrum of a: magnesium stearate, b: crospovidone, c: sodium lauryl sulfate and d: microcrystalline cellulose.

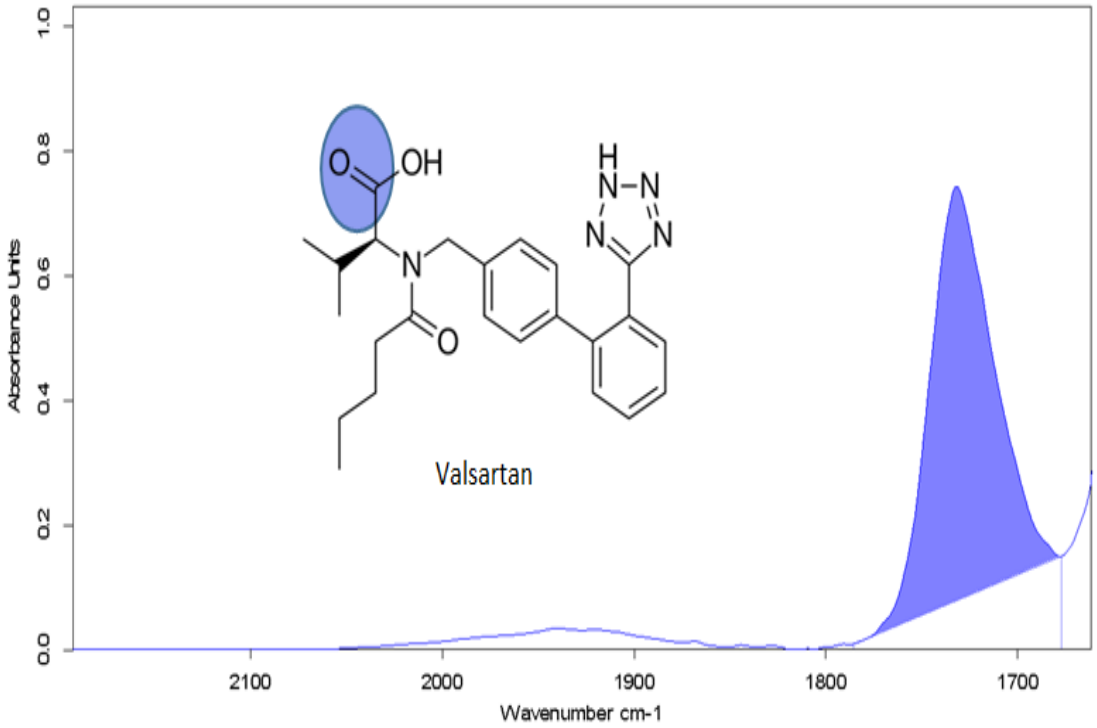

Fig. 5: FT-IR spectrum of pure valsartan at the chosen peak (1732 cm−1) for quantitative analysis.

Correlation value

The correlation value is a measure for the similarity between the two spectra : reference spectrum and sample spectrum[31].

In order to check whether the samples are compatible with the specific quality standard, a comparison of the spectrum obtained from valsartan working standard (reference) and valsartan capsule (sample) was performed to verify the similarity between them. The result of a quick comparison was (Ok) with correlation value equivalent to 95.71% (Figure 6).

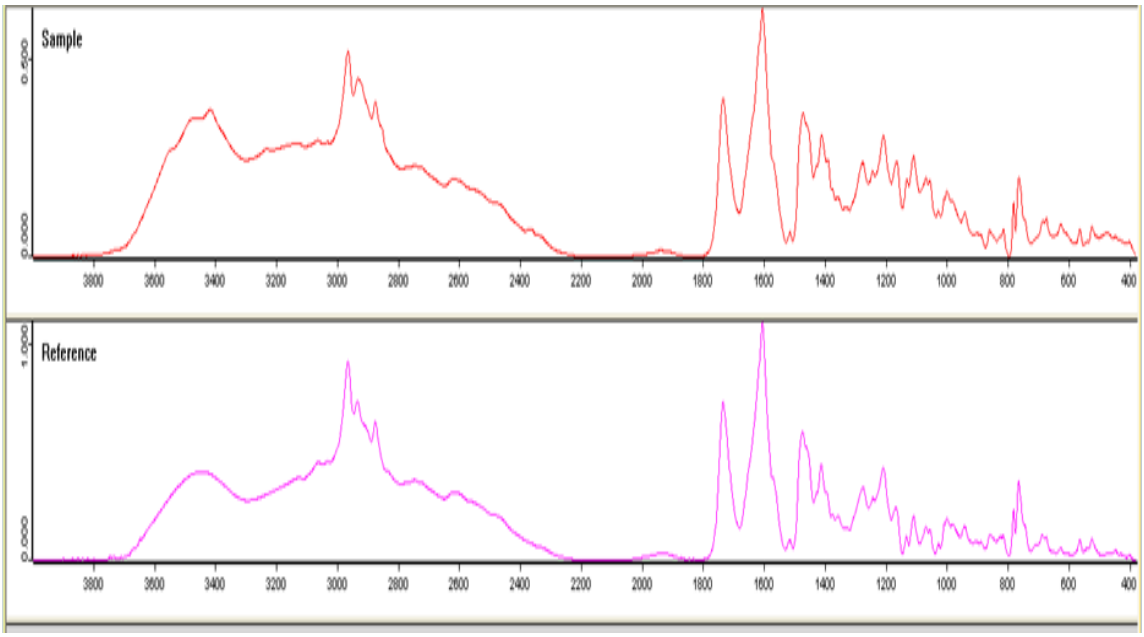

Fig. 6: Correlation value between valsartan working standard (reference) and valsartan capsule (sample)

Method validation

Validation of the developed method was carried out regard to the following parameters: linearity, accuracy, precision, robustness and selectivity depending on the international conference on harmonization (ICH) recommendations[32,33,34].

Linearity and range

linearity of an analytical method can be defined as its possibility (within a given range) to acquire test results which are straightforwardly corresponding to the concentration of the sample[32].

To validate the linearity of the method, five different concentrations of working standard valsartan (0.5 to 2.5% w/w) were used and evaluated on three different days. For the preparation of the disks, the amounts equivalent to 0.5,1.0, 1.5, 2.0, and 2.50 mg of valsartan working standard (previously diluted in potassium bromide of 1:10) were obtained and diluted with sufficient amounts of KBr to achieve 150 mg disks. For each calibration standard, three samples were prepared and the average of three measurements was used to construct the calibration curve. The FT-IR spectrum for the diluted valsartan samples of various concentrations is shown in (Figure 7).

The representative line was established for the relationship between the absorbance obtained for a carbonyl peak versus the corresponding concentration of the drug. Then, the correlation coefficient (r) was calculated to estimate the method's linearity. Perfectly, the calibration curve should be linear with a value (r) of 0.999[32]. Regression line of valsartan with the regression equation and correlation coefficient was shown in (Figure 8).

The correlation coefficient (r) was 0.997. The result showed excellent correlation within the tested concentration range and suggested the linearity of the proposed method over the range (0.5–2.5% w/w) for valsartan.

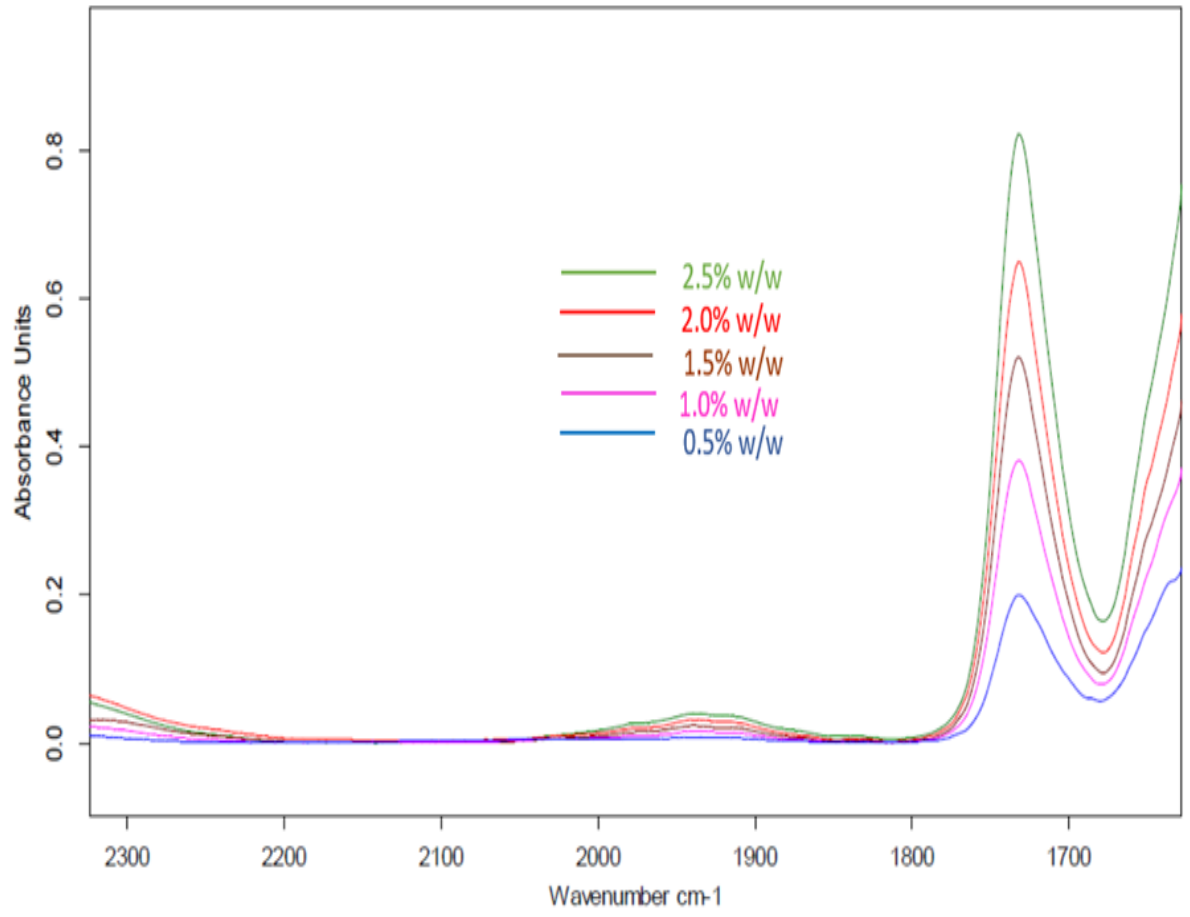

Fig. 7: Response of the carbonyl peak (1732 cm−1) to various concentrations of the valsartan working standard by FT-IR spectroscopy.

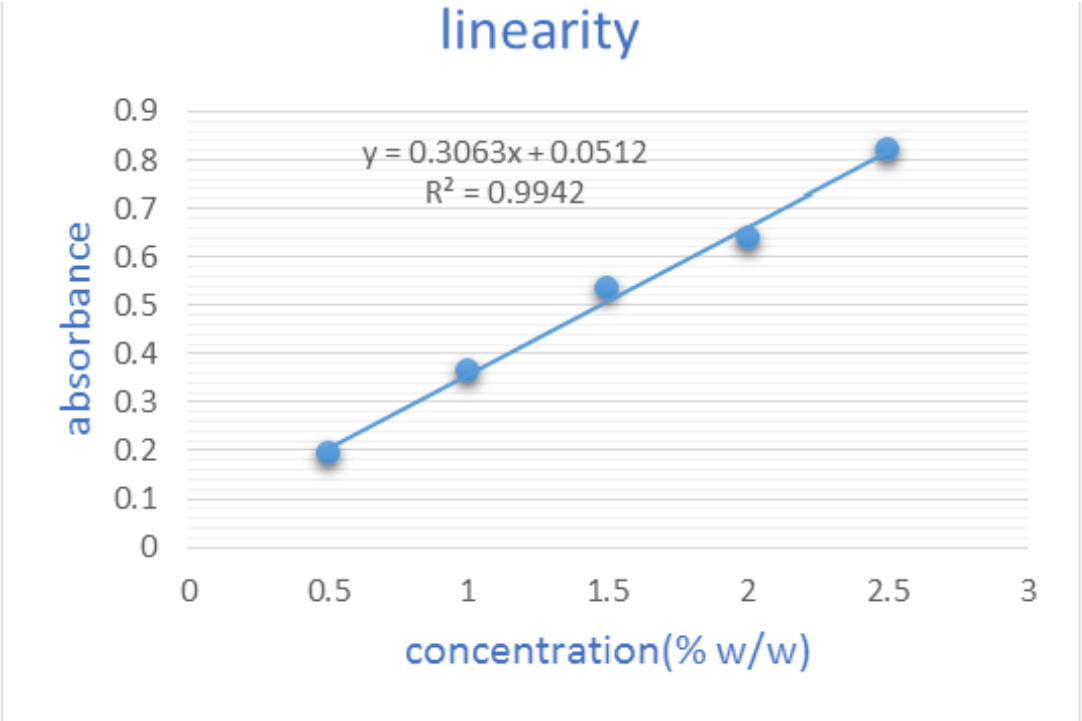

Fig. 8: Linearity of valsartan.

Accuracy

Accuracy of analytical procedure is the proximity between the real value and the value obtained in the analysis[32].

The accuracy of the assay method was estimated by standard addition method at three levels (80, 100 and 120%) of the working concentration of the method (2%w/w) in triplicate. A stock mixture containing valsartan was prepared at a concentration of 1:10 in KBr. In three different disks of 150mg, the amounts of 0.6, 1 and 1.4 mg of standard mixture were added with 1 mg of sample mixture (diluted 1:10 in KBr) and made up to 150 mg with KBr. Final concentrations were 1.6, 2, and 2.4 mg which correspond to 80, 100, and 120% of the target concentration, respectively. Table 1 illustrates the method of disk preparation for the recovery assay. Accuracy was evaluated by recovery of pure drug from excipients. Table 2 shows the accepted range, recovery and RSD% value for the studied drug.

Recovery of valsartan ranged between (98.1% and 101.44%). The relative standard deviation (RSD%) value was 1.8 which was less than 2%. The mean recovery value was among the acceptable range of accuracy (98–102%). Hence, the recovery of the developed method was deemed acceptable and the presented method was accurate and usable to the determination of valsartan.

Table 1: Preparation of disks for the recovery assay of the proposed FT-IR method for valsartan analysis.

Preparation method	Sample Valsartan (1:10)	Reference Standard Valsartan (1:10)	Final theoretical concentration (% w/w)	Potassium Bromide (KBr) (mg)	Recovery %
Sample	10	-	1	140	
R1	10	6	1.6	134	80
R2	10	10	2	130	100
R3	10	14	2.4	126	120
Reference Standard	-	10	1	140	

Table 2: Accuracy of the developed FT-IR spectroscopy method.

	R1	R2	R3
Absorbance	0.5443	0.64	0.7955
	0.5443	0.6666	0.8085
	0.5504	0.65	0.7863
Concentration (% w/w)	1.609	1.9222	2.4299
	1.609	2.0091	2.4742
	1.6297	1.9549	2.3999
Mean	1.6159	1.962	2.4346
Theoretical concentration(% w/w)	1.6	2	2.4
Recovery %	100.99	98.1	101.44
Mean recovery % ± SD	100.17 ± 0.018		
RSD%	1.8		
n = 3			

Precision

Precision is the proximity of results when a series of measurements are obtained from different samples of the same sample[32]. There are various levels of precision including repeatability, intermediate precision and reproducibility.

The precision of the developed method was assessed by repeatability and intermediate precision.

Repeatability was assessed by analyzing six consecutive disks for the valsartan working standard at a concentration (2% w/w) on the same day and under the same working conditions. Then, the percentage relative standard deviation (RSD%) between the absorbance values was calculated as shown in Table 5. Ideally, the RSD% value should be less than 2% which was the case for our experiment showing an RSD% value of 1.66 (Table 3).

Intermediate precision was performed by repeating the assays on two different days. Three replicates at three concentrations of 0.5, 1.0 and 2.0% w/w were prepared and assayed. The percentages of relative standard deviation (RSD%) of the absorbance for each concentration on the first day and for two consecutive days were calculated. Ideally, the RSD% values should be less than 2% and 5% for first and two consecutive days, respectively.

On the first day, RSDs% values were 1.85,1.99 and 1.23 for the concentration 0.5, 1.0 and 2.0% w/w, respectively and for two consecutive days, RSDs% values were 4.37,3.08 and 3.22 for the concentration 0.5, 1.0 and 2.0% w/w, respectively (Table 4).

Given that the RSDs% values were less than 2% for first day and less than 5% for two consecutive days, it can be concluded that the results were precise for the study.

Table 3: Repeatability of method.

Concentration (% w/w)	2					
Absorbance	0.6226	0.6296	0.621	0.6356	0.6359	0.6498
Mean* ± SD	0.6324±0.0105					
RSD%	1.66					
*n=6						

Table 4: Intermediate precision of method.

	Concentration (% w/w)	Absorbance			Mean absorbance ±SD	RSD%
First day	0.5	0.1935	0.1999	0.1997	0.1977 ± 0.0036	1.85
	1	0.376	0.3721	0.3617	0.3699 ± 0.0073	1.99
	2	0.6498	0.6364	0.6359	0.6407 ± 0.0078	1.23
Second day	0.5	0.2074	0.2126	0.2174	0.205 ± 0.0089	4.37
	1	0.3513	0.3819	0.3607	0.3672 ± 0.0113	3.08
	2	0.6186	0.6124	0.6686	0.6369 ± 0.0205	3.22

Robustness

Robustness aims to ensure that the analytical method is not affected by small changes in analytical parameters[32].

The following parameters were manipulated: compression time of disks (2min above and below the working compression time), total disk weight (2 mg above and below the working disk weight) and compressive strength (2 ton above and below the working pressure). Thus, three disks of valsartan working standard at a concentration of (2.0% w/w) were analyzed under each previously described condition. Similarity of the results was evaluated according to the (RSD%) among the measured absorbance for each variation. (Figure 9) displays the results as a chart. The RSD% values were less than 5%, denoting the robustness of the analytical method for the analysis of valsartan by FT-IR spectroscopy.

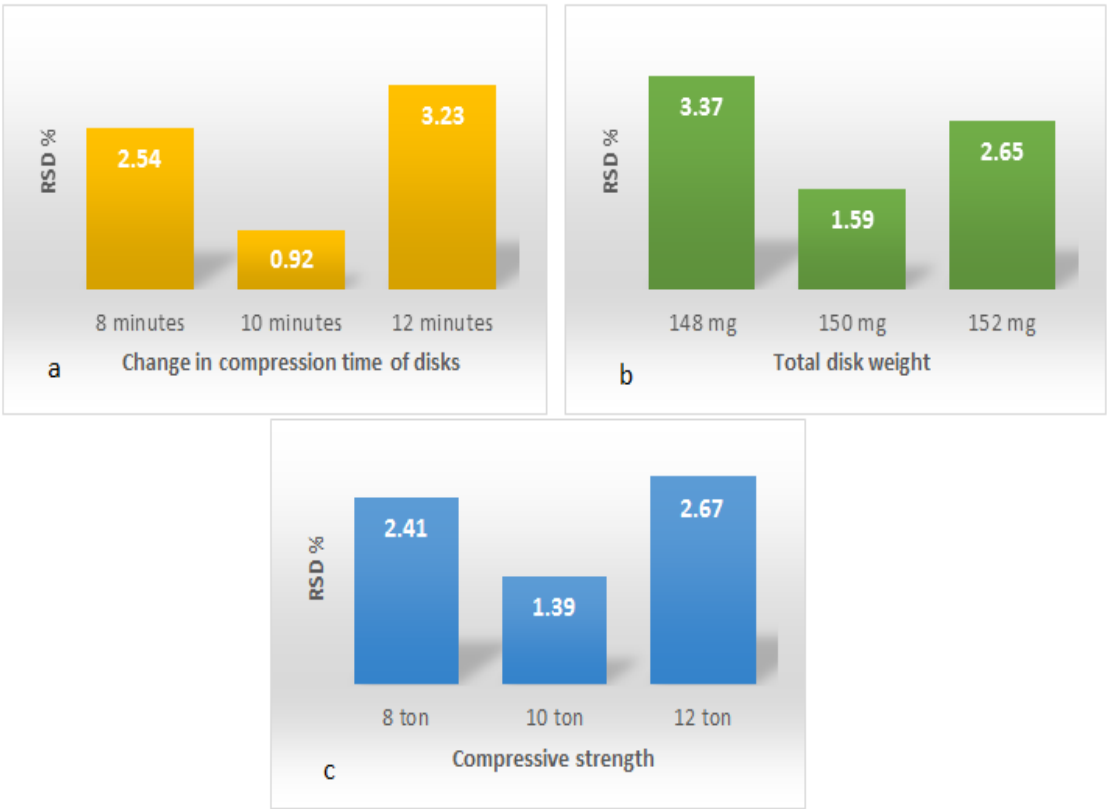

Fig. 9: Bar charts represent the difference in the relative standard deviation (RSD%) for a) change in compression time of disks, b) total disk weight and c) compressive strength.

.**Selectivity**

Selectivity is the ability to accurately and precisely measure a drug in the presence of other components, which may be in the sample matrix[32].

To assess selectivity, the spectrum of working standard valsartan was compared with the spectrum of each excipient present in the pharmaceutical dosage forms including sodium lauryl sulfate, microcrystalline cellulose, crospovidone and magnesium stearate.

The spectrum of working standard valsartan and excipients are presented in (Figures 2 and 4). No interferences were noticed in the chosen range selected for quantitative analysis (1777.38-1680.94 cm^{-1}), thus confirming selectivity of the studied method.

Application of our developed FT-IR method for content determination of valsartan in the marketed pharmaceutical dosage forms:

In order to check the suitability of the developed method for the quantitative determination of drug concentrations (either alone or in binary mixtures) within solid pharmaceutical dosage forms, two solid pharmaceutical forms were analyzed. First pharmaceutical dosage form was capsules containing valsartan as a sole ingredient, while second pharmaceutical dosage form was tablets containing valsartan in a binary mixture where the isolated peak of valsartan for the quantitative analysis did not interfere with other compounds in the mixture. The best peak selected for the measurement confirmed the linearity and selectivity tests, concurrently. Other parameters such as accuracy, precision and robustness tests were also conducted. (Figure 10 and Figure 11) reveal the complete spectrum of the capsule and tablet dosage form, respectively. Quantification was carried out in triplicates based on the absorbance of the chosen peak at 1732 cm^{-1}. The obtained results are shown in Table 5.

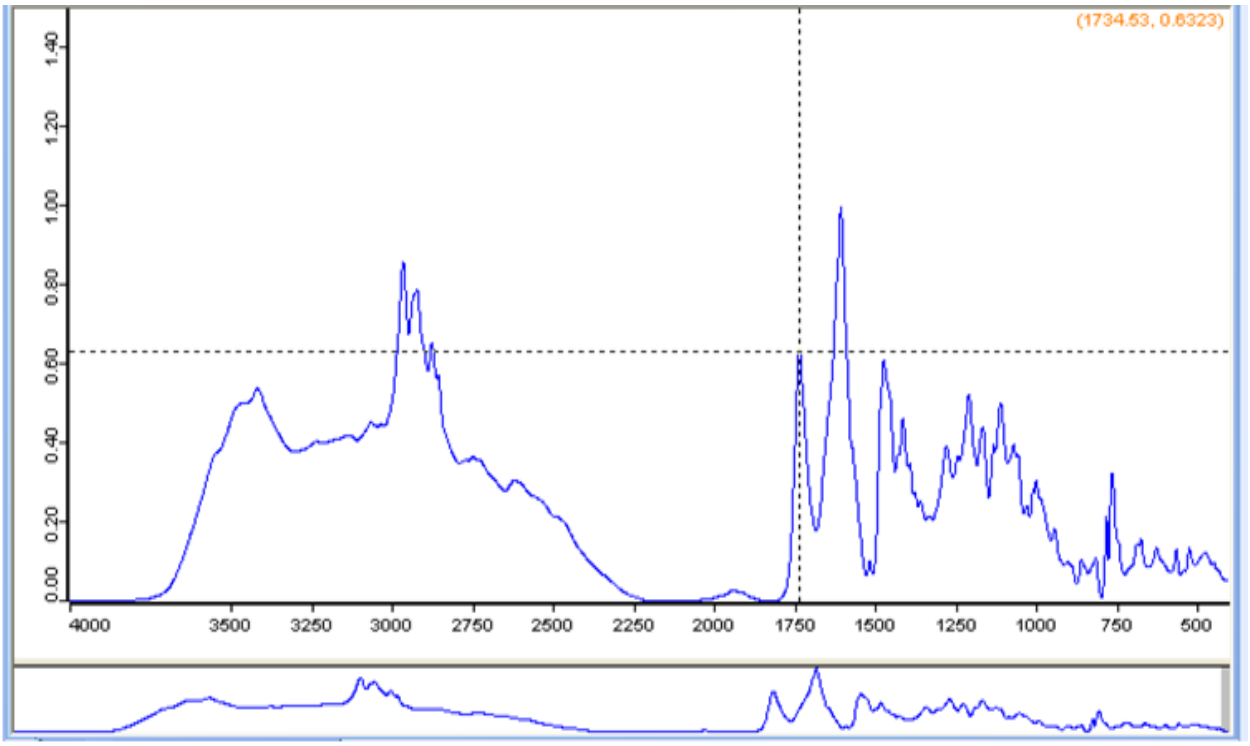

Fig. 10: FT-IR spectrum of valsartan in capsule in the mid region after the application of the optimal conditions (Total disk weight 150mg, compression time of disks 10minutes and compressive strength 10ton).

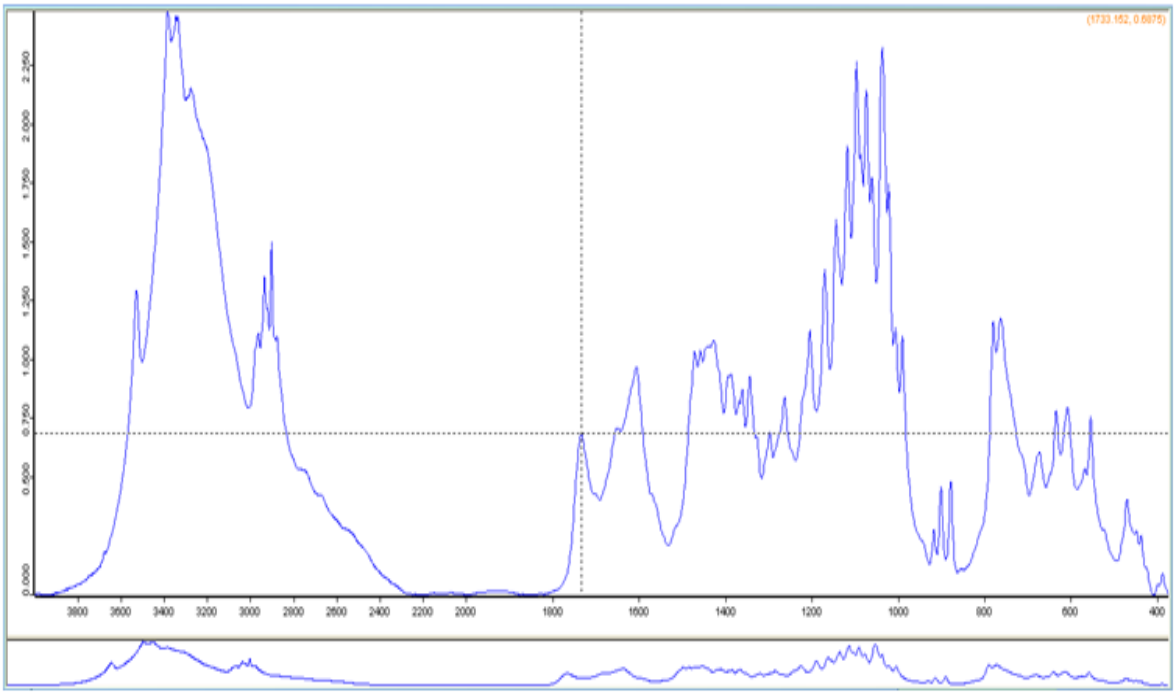

Fig. 11: FT-IR spectrum of valsartan in tablet in the mid region after the application of the optimal conditions (Total disk weight 150mg, compression time of disks 10minutes and compressive strength 10ton).

Table 5: Results of pharmaceutical assay using the developed FT-IR spectroscopy method.

Active ingredient and potency	Valsartan 160mg	Valsartan 160mg
Pharmaceutical form	capsule	tablet
Units Number	20	20
Absorbance	0.6313	0.6875
	0.6262	0.6613
	0.65	0.6702
Found values (% w/w)	1.8938	2.07
	1.8772	1.99
	1.9549	2.02
Mean ± SD	1.9086±0.04	2.02±0.01
RSD %	2.14	1.99
Theoretical concentrations (% w/w)	2	2
Content %	95.43	101

Regarding to capsule, the determined concentration was found to be 95.43% and was fully matched with the labeled content. It is within the acceptable range mentioned in the British Pharmacopeia of 95%–105%[35]. The relative standard deviation (RSD) value was less than 5%.

On the other hand, the determined concentration of valsartan in combination (valsartan + amlodipine) was found to be 101% and was fully matched with the labeled content. It is within the acceptable range mentioned in the United States Pharmacopiea of 90%–110%[36]. The relative standard deviation (RSD) value was less than 5%.

Conclusion

FT-IR spectroscopy may have the potential to serve as a useful technique for qualitative and quantitative analysis of pharmaceuticals. The present study confirmed the potential of FT-IR spectroscopy technique in routine analysis of valsartan which offers various advantages in terms of being a rapid, cheap, eco-friendly, and including relatively simple sample preparation. Hence, the developed validated method provides a good alternative to chromatographic methods in quality control laboratories.

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مطيافية الأشعة تحت الحمراء باستخدام تحويل فورييه للتحديد الكمي للفالسارتان في المواد الأولية والأشكال الصيدلانية

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يوضح هذا البحث التطبيقات المحتملة لمطيافية الأشعة تحت الحمراء باستخدام تحويل فورييه (FT-IR) في التحليل الصيدلاني. تم تطوير طريقة طيفية بسيطة وسريعة وغير مدمرة وخضراء باستخدام (FT-IR) لتقييم جودة الفالسارتان ، باستخدام بروميد البوتاسيوم (KBr) كمدد لتحديد كمية الدواء في المواد الأولية وفي بعض الأشكال الصيدلانية. تم تجنب التحضير المعقد والطويل للعينة باستثناء الطحن لتشكيل القرص واستبعد استخدام المذيبات العضوية. تم الإعتماد على الامتصاصية التي تم الحصول عليها لقمة الكربونيل (C = O) عند ١٧٣٣ سم -١ لتطوير منحنى المعايرة بناءً على قانون بير لامبرت البسيط.

تم إجراء التحقق من صلاحية الطريقة وفقاً لإرشادات المؤتمر الدولي للتنسيق (ICH). تم تقييم الخطية والصحة والدقة والمتانة والنوعية وأظهرت نتائج مقبولة للتحقق من صحة الطريقة في مجال التركيز (٠.٥ - ٢.٥٪ وزن / وزن).

كانت الطريقة المطورة والمثبتة مناسبة لمراقبة الجودة وذلك بتحليل الفالسارتان في المواد الأولية وفي المستحضرات الصيدلانية.