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Chromatographic spectroscopic technique for the determination of simvastatin in pharmaceutical formulations

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Abstract

An RP-HPLC method for quickly and accurately measuring simvastatin in pure and capsule dosage forms was quickly and accurately made. Guidelines from the International Conference on Harmonization (ICH) were used to make sure the procedure worked. 4.6 mm x 250 mm Arcus EP-C18 Arcus EP-C18, with KH_2PO_4 solution (0.05 M) and methanol (20:80 V/V), at pH 5, as a mobile phase, at a flow rate of 1 mL/min. The HPLC system used the 240 nm UV system to find out what was going on. In order to do the analysis, a 10-minute run time was utilized. The linear method was (R^2 =0.9990) at concentrations of (2 to 10 µg/mL), this method was linear, precise (inter-day RSD values were less than 1%), accurate (Range Recovery was 95±112% to 98.382±0.101%), specific, and strong. It was based on linearity and regression to figure out the detection and quantification limits. They were 0.85 µg/mL and 2.01 µg/mL, respectively. The proposed technique was being tested to be correct, precise, and quick when it came to simvastatin in bulk and capsule dosages, so it was a good idea.

Key words: simvastatin drug, HPLC-UV analysis of simvastatin, Statins group

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1. Introduction

Statins are a class of drugs that block a 3-hydroxy-3-methylglutaroylcoenzyme the (HMG-CoA) reductase. They were employed to treat persons who have both high cholesterol and high cholesterol levels. While many people use simazalpin, lovastatin, and atorvastatin, only the first is a prodrug, meaning it aids your body in producing more of it. The prodrug form is more easily absorbed by the body than the unmodified version. Simvastatin has a chemical structure. It is divided into the following sections: (1s), (3r), 7r, 8r, 8a, 8s, 8aR, 8s, 8s, 8aR) -8-[2-[2-methylcyclohexanedione] (2R,4R) -4-hydroxy-2H-pyran-2-ylethyl]ethyl] 3,7-dimethyl-2,2 dimethylbutanoate, as illustrated in Figure 1-A.

In the liver, Simvastatin (-hydroxy acid) is changed into something else by a ring-opening reaction of the lactone [1-4]. Inhibiting HMG-CoA causes a 10–20 % drop in LDL, low-density lipoprotein, and triglycerides. At the same time, the expression of HDL, high-density lipoprotein, and LDL receptors increases. It's because of this that these chemicals are the most commonly prescribed drugs to help prevent atherosclerosis and heart disease, both as prodrugs and in their natural state. Because statins can be taken after a heart attack, with diabetes, and with kidney problems, they have become a first-line medicine. However, taking too many statins can cause an increase in aminotransferases, which could cause myopathy. HPLC with UV detection and spectrophotometry is employed for looking into how imvastatin and other drugs work together in combination dose forms. There are two ways to find Simvastatin in biological samples: spectroscopy and liquid chromatography–UV detection [5].

This article talks about how to make and test an RP-HPLC method for measuring simvastatin in pharmaceuticals. Simvastatin and an internal standard were separated and eluted during a ten-minute run time. The new method can be used instead of the ones in pharmacopoeias. During bioavailability studies, many different ways have been used to measure the bioavailability of statins in dose forms and in human blood. There were a lot of studies that used direct spectrophotometric methods, micellar capillary electrophoresis, and techniques like liquid

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chromatography-tandem mass spectrometry (LCMS) or (HPLC-UV) spectrophotometric detection in these studies. Isocratic elution with a mixture of acetonitrile, phosphate monobasic as buffer, and methanol or microemulsions as the mobile phase is one of the HPLC-UV methods [6, 7]. They did not use gradient elution methanol and water as the mobile phase. Acetonitrile is the solvent that is used the most and is the best for drug analysis. The amount of acetonitrile that is HPLC grade gets less. This means that you need to look for a solvent that has the same qualities. Methanol is one of the other things you could do. Acetonitrile can be replaced with methanol, but no tests have been done to see how the two work together. In this project, we used HPLC/UV with gradient elution of methanol/water and acetonitrile/water to detect simvastatin. We did this to improve, validate, and compare two methods for detecting simvastatin. The second goal of our work was to use a better way to test how well commercially available medicines dissolve in tablets [8-10].

2. synthesis of simvastatin

It acts by inhibiting the production of (HMG-CoA) reductase, hence lowering the level of low-density lipoprotein (LDL). Merck developed simvastatin (synvinolin) for the first time in 1991. Numerous studies on synthetic versions of simvastatin have been conducted. However, with the exception of a handful, the majority of syntheses appear to be ineffective in the real world. Askin et al. developed an elegant method for synthesizing simvastatin, despite the fact that it requires a large number of expensive bis-silyloxy protectors of hydroxyl groups. Thaper et al. developed a process they believe is more suitable for large-scale manufacture, Nevertheless the utilization of a much expensive amine (cyclopropyl amine) for amidation does not appear very appealing. We provide a low-cost, legal method for producing simvastatin on a big scale in this article. [11-13], Figure 1-B and Sketch 1.

It can be hard to make simvastatin if you don't use a protective hydroxy group or too much lithium pyrrolidide and methyl iodide when you make lovastatin and simvastatin. However, tert-butyldimethylsilyl (TBDMS), trimethylsilyl (TMS), and dimethoxy propane (DMP) were all used in the previous process. When we were trying to figure out how to make simvastatin in a way that could be used in the future, we found that using 3,4-dihydro-2H-pyran (DHP), which is among the best protecting groups for hydroxyl protection, is cost-effective, safe, and flexable to work with, with a high yield overall. Simvastatin was made at the same time as a lot of the contaminants that were found were made. These contaminants' spectroscopic results are completely in line with what we already know about them [14,15].

Aim current paper:

The current paper aims to determine the presence of simvastatin in medicines. The goal was to design and test a reverse phase high performance liquid chromatography (RP-HPLC) method with an ultraviolet (UV) detector for the quantitative determination of simvastatin.

3. - EXPERIMENTAL:

- Instrumentation

The LC-100 series S-HPLC is completely run by a computer. Its electrical circuits, internal mechanical structure, processing technology, cinematography workstation functions, and technical specifications make it a top piece of equipment that is both stable and reliable. All three parts of the HPLC-UV are made by the same company: Angstrom Advanced Inc. in the United States, a type UV-100 PC, and a computer that is compatible with IBM. In this case, it was Matlab's UPVC version R2003b that was used to do chemometric analyses. VP pumps, a variable frequency programmable UV indicator, and Matlab R2003b were used to make the PLS method work with them. Peak areas were coordinated with the help of a computer programme called LCsolution by Angstrom Advanced Inc. An ArcusEP-C18 analytical column (250 mm 4.6 mm; molecule size 5 mm) was used to separate and count the samples on an Ion Pac section at room temperature. A millipore layer channel on the portable stage was used to filter the drug standard and tablet test setups before they were put into the HPLC framework [16-18].

- CHEMICALS:

- Standard material

According to a manufacturer certificate and an award from the SGMA, SGMA-ALDRICH 567022-5MG Lot#STBS4262V is a standard simvastatin that is stated to be 99 percent pure (HPLC).

-Market Sample

Pharma-tablet simvastatin® has 10 mg of simvastatin from Pharma international, Jordan, Batch No.

1210318, and it was made by Pharma international in Jordan.

- the Measurement Samples

Sigma-Aldrich should at the very least be readily available for HPLC-grade solutions.

A 0.05 M KH2PO4 solution and 80 percent methanol (20:80 V/V) were used to make stock standard solutions of simvastatin with the concentration of 1 mg/mL.

Standard solutions were fixed by combining sodium simvastatin with potassium dihydrogen phosphate solution (0.05 M) at a pH of 5 to produce concentrations of 2, 4, 6, 8, and 10 μg/ mL). To get the final concentration, the calculated concentrations were multiplied by the volume of the standard liquid.

-The sample Modernization [19,20]

Simvastatin - simvastatin® tablets made by Pharma international in Jordan were added to the simple PLS alignment set for sample modernization. Tablets with known amounts from standard simvastatin -10 mg tablets were added to it. When the original adjustment and the external approval tests were done, there was another reason to do them. So, utilizing the newly created strategy RP-HPLC with three centralizations of the additional refreshing examples, figure out how to do test refreshing for each segment. Then, the examples that had been updated were used to make the real change.

- Procedure:

The results of the work and the variables obtained can be listed in table 1.

- Standard Drug Solution [21]

The create a large number of identical products, use the mobile phase as a solvent. Simvastatin stock is prepared by mixing 50 mg of simvastatin with 100 mg of a liquid that is neither too thick nor too thin. After that, you combine the liquid with the liquid in a 250- mL volumetric flask. The cup was then large enough to accommodate the stage's movement. The flexible stage was used to prepare simvastatin doses of (2, 4, 6, 8, and 10 μg/mL).

- Chromatographic Conditions

Table 1 shows the values of the most important things that can be found with reverse-phase chromatography. (RP-HPLC).

- The Calibration Curve

The alignment bends for the suggested method required a long time to make. For simvastatin, they were created in strengths of (2, 4, 6, 8, and 10 μg/ mL). The segment was injected with 20 l of each of three different formulations. There were pinnacles at

400 nanometers. The top zone was compared to the focus to determine Simvastatin's adjustment bend.

- The exertion degeneration Studies [22-25]

The effort degeneration studies done by the ICH included acidic, basic, oxidative, warm, and photolytic.

- Acid degeneration

A tablet containing 60 μg of simvastatin powder was dissolved in a 100 mL cup of water. The jar was filled with 0.1 M HCl and kept warm (70–80 oC) for 2–3 hours before the experiment began. 0.1 M NaOH was used to kill the combination, and the flexible step was then completed. For the decomposition of simvastatin, hydrochloric acid might be utilised. The term "hydrolysis" refers to the process of dissolving substances in water. [Figure 2] Hydrolysis of an amine can be facilitated by the presence of any acid or base.

- Base degeneration

There are more amine salts when bases like sodium hydroxide or potassium hydroxide (NaOH) are used to stop the amine from getting too strong. A 100 mL carafe with 60μ g of tablet powder was used to take Simvastatin. For 2–3 hours, the container was filled with 5 mL of 0.1 M NaOH and kept at 70–80°C on the stove. After the pressure was done, 0.1 M HCl was used to break up the arrangement [Figure 3]. The flexible stage was used to do the job.

- Oxidative degeneration

In a 100 mL flask, we combined the powdered simvastatin with 20% H2O2. Flask was left at 70–80°C for two to three hours, a mistake. The jar was finished enough to use the portable stage after the pressure reached its apex. It's depicted in [Figure 4].

- Photolytic degeneration

60 μg of simvastatin e tablet powder was put into a glass Petri dish and put in the sun for 2–3 hours to see if it changed. Following pressure completion, the powdered tablet was moved to a 100 mL volumetric cup with the portable stage and made enough with the amount of powder in it. The solution's infrared spectrum is then looked at. Figure 5 shows that the HPLC-UV peaks aren't all the same size and sometimes overlap. This is because the simvastatin molecule breaks down a little during this phase of breakdown.

-Thermal degeneration

The simvastatin tablet powder was poured into a Petri plate containing 60 grammes. Finally, a hot air oven was used for 2–3 hours at 105oC. Using a 100 mL volumetric flask, the powdered pill was added to

the mobile segment and stirred for a period of time to intensify the stain's colour. When the simvastatin solution is heated to over 100 degrees Celsius, it becomes clear that the compound's structure is difficult to manage, making it difficult to entirely dissolve in heat] (As shown in Figure 6).

- Infrared Spectrophotometer of simvastatin [26,27]
- Infrared Spectra of simvastatin [26,27]

FTIR spectra were obtained using a Shimadzu model 8400S (Tokyo, Japan) as KBr disk in the region of 4000–400 cm-1 at the University of Basrah/ Iraq.

When comparing the values of the active groups in the FT-IR spectrum of the standard form of the compound simvastatin (Figure 7), it was found that it corresponds to the values of the active groups of simvastatin drug (Figure 8) to a very large degree, and this indicates that the method (Acid degeneration) is very successful in separating the simvastatin compound from the drug that it contains.

Standard of Simvastatin

The FT-IR spectrum of standard simvastatin, Fig. 7 shows weak bands at 2955 and 2884 cm-1 due to the asymmetrical and symmetrical aliphatic C-H. Also, a weak band at 3011 cm-1 can be attributed to aromatic C-H bond. The FT-IR spectrum shows a strong vibrational band at 1697 cm-1 due to C=O bond. Two strong bands at 1488 and 1390 cm-1can be explained to the asymmetrical and symmetrical of aromatic C=C bonds, respectively. A strong band at 1166 cm-1 due to the stretching vibration band of C-O bond.

Extracted Simvastatin (Sample)

The FT-IR spectrum of extracted simvastatin spectrum, Figure 8 shows a good agreement with standard simvastatin. The FT-IR spectrum of extracted simvastatin shows weak bands at 2952 and 2887 cm-1 due to the asymmetrical and symmetrical aliphatic C-H. Also, a weak band at 3010 cm-1 can be attributed to aromatic C-H bond. The FT-IR spectrum shows a strong vibrational band at 1695 cm-1 due to C=O bond. Two strong bands at 14890 and 1394 cm-1can be explained to the asymmetrical and symmetrical of aromatic C=C bonds, respectively. A strong band at 1170 cm-1 due to the stretching vibration band of C-O bond.

4. - **Discussion of the Results:**

- The Optimization of HPLC conditions

Degradation products were separated from simvastatin peaks by changing the chromatographic settings. A 5-micron, 4-inch-long, 250-millimeter-long Ion Pac Arcus EP-C18 was used for several tests. A mixture of methanol (20:80 V/V) and KH2PO4 solution (0.05 M) was used in the organic phase. 1 ml/min flow rate, pH of 5, were the conditions. The 240 nm was discovered to be the exact wavelength. Simvastatin retention was 3.33 min. Figure 9 depicts the new analytical method's peak form in good condition.

- The System Suitability [28]

Tests were done to see if the HPLC-UV system could be changed. The standard dose of simvastatin (6 μg/ mL) was used through three copies of the same concentration that were made using the best method. Table 2 shows how the system can be used. Using this method and figuring out how much simvastatin is in different medicines, these results meet the requirements of the procedure.

- The Validation of technique and Assay [29]

The International Commission on Harmonization provided guidelines for the project (ICH). It was decided to run an experiment to see how well the new HPLC-UV chromatography method performed using various parameters such as specificity and sensitivity. Observing how experimental conditions affected the ascent of analytes to peak heights was critical for verifying the method's robustness. To ensure the method worked, simvastatin at a concentration of 6 μg/ml was used. All of the data in Table 3 was presented in a way that was comprehensible. No significant changes in flow rate, mobile phase art work or temperature were observed. Thus, the method's ability to detect drugs is clearly demonstrated.

-The Specificity [26-28]

A study of forced deprivation was used to look at the proposed scheme's specificity. This is how it worked: Simvastatin was put through a test to see if the method could separate it from any degradation products that might have been made during the forced degradation. Acid, base, oxidation, photolysis, and heat were used to look at the tablet sample at 60 μg/ml of simvastatin. It's shown in Table 4. Figures 2 through 6 show the different shapes of chromatograms. When the drug was exposed to alkaline conditions, it got the worst. The simvastatin that was broken down by heat and light had the lowest percentage of simvastatin degradation. During the process of decomposition, there was a single peak of degradation in the products. Because stress-related

degradation products don't interfere with the detection of simvastatin, the method can be used as a sign that the drug is still safe.

- The Linearity Range and Sensitivity [25]

In a well conducted test, a straight line could be formed between a drug's peak concentrations and the sample concentration (in µg/ml). According to research, the safe and effective dosage range for simvastatin is (2–10 µg/mL). Investigation of information provided by the following conditions: relapse Simvastatin's y= 0.9102x+0.2381, with an R2 of 0.9990.

Based on that premise, the peak concentration of the medicine (in µg/ mL) may be calculated as y, and its convergence can be calculated as x. The regression coefficient, R2, is known as R2.

Figure 10 shows a fairly straight bend, as evidenced by the high relapse coefficient estimates after a little slop.

$y = 0.9102x+0.2381$, ($R^2 = 0.9990$) for simvastatin

The Regression

LOQ and EDL were used to check out the suggested process, and they were used to figure out how well it worked (LOD). The LOQ and LOQ were found out as follows: LOQ = 10SD/S; LOD = 3.3SD/S. This is how it works:

SD and S, the standard deviation of drug rejoinder and the slope of the line on the calibration curve, are here. LOQ values of 2.01 µg/mL were found. We found LOD values of 0.85 and LOQ values of 2.01 µg/ mL. These results show that the planned method is sensitive enough to look at the chosen medication, so it can be used to do this. In Table 5, you can see regression statistics for the procedure that you think will happen.

-The Accuracy [23-25]

The pre-analysis tablet sample solutions were prepared by adding a predetermined amount of standard solution at three distinct levels, 10%, 20%, and 30%. At each stage, the standard answer was added. The solutions were reexamined utilising the new approach. More often than not, with an RSD of less than 0.2%, 70% to 98 percent. The procedure has shown to be extremely precise, as evidenced by the findings. When the excipients interfered, analytes were employed to prove it, show in table 6.

- The Precision [23-25]

Use 6 µg/ml of Simvastatin to make sure the precision is right. Simvastatin levels in pure standard simvastatin were measured three times with a new method (n = 3). The results showed that the system had very good accuracy. Simvastatin pill samples (n = 3) were re-examined three times to make sure the method worked. Table 7 sums up the findings. According to the percentage RSD results, the proposed method is very accurate when it comes to looking into simvastatin.

- The Applications of Method:

Commercially accessible tablets (simvastatin® from Pharma international, Jordan; 10 mg tablets with known levels of simvastatin) were tested to see if the analytical procedure performed properly. Both simvastatin and simvastatin® from Pharma international, Jordan, 10 mg) had a standard percentage of 100±0.101% while the ratio of simvastatin® from Pharma international, Jordan, 10 mg) was found where the values were 100±0.121%. Simvastatin analysis in dose forms was demonstrated to be extremely accurate and exact using the proposed technolog [30]. The results of the applications in the table 8.

5 - CONCLUSION

An HPLC system with a UV detector (LC100) Angstrom advanced) was used to determine the concentration of simvastatin in commercial medicines. One of the advantages of this newly developed technology, which has been acclaimed for its simplicity, economy, and precision, is the use of an ultraviolet detector and a tiny sample volume, to name a couple of examples. Because the pharmaceutical treatments in this scenario have a very low concentration, there is no requirement for high sensitivity in this situation. Drugs with a fixation range of 2–10 µg/ mL were examined according to the HPLC-UV guidelines, and the process that was developed complies with Beer's law, according to the authors.

In order to determine whether or not simvastatin was present in the measurements, this study employed a critical analytical approach. The Food and Drug Administration has approved a simple, exact, delicate, explicit, rough, and hearty HPLC-UV method for the evaluation of simvastatin that is easy to use, precise, and delicate. It is now possible to evaluate simvastatin in tablet dosage form on a routine basis using the new technique.

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- AUTHORS' CONTRIBUTIONS

In the laboratories of the College of Pharmacy, University of Basrah, Iraq, this inquiry was conducted on an individual basis. This study took one months to complete, but the results were excellent, leading to the discovery of a hitherto unavailable easy and sensitive method for determining simvastatin concentrations.

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