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NOVEL CHEMICAL METHODS FOR IDENTIFICATION AND DETERMINATION OF TRIPTANS IN PHARMACEUTICAL PREPARATIONS

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Abstract: Triptans referred as 5-HT1-receptor agonists are groups of medicines, that are utilized to treat migraine and certain other headaches. İn this study, zolmitriptan and Sumatriptan as a selective serotonin receptor agonist for the 1B and 1D subtypes have been studied. This study was conducted to investigate the qualitative determination of triptan drugs (sumatriptan and zolmitriptan) from their pharmaceutical preparation by using oxidation coupling reaction. We studied the interaction of drugs by using five different type of coupling reactions in the presence of potassium permanganate as an oxidizing agent. The final product was analysed under Uv-VIs spectrophotometer, and it was found that, the resultant product of zol-shc, zol-azo, zol-oxi, zol-chro and zol-blrch give maximum absorbance at 510 nm, 540 nm, 490 nm, 520 nm, 505 nm of wavelength repectively, compare to zolmitriptan at 240 nm. Similar results were observed for suma-shc, suma-azo, suma-oxi, suma-chro and suma-blrch 525 nm, 540nm, 515 nm, 530nm, 520 nm and 480 nm of wavelength respectively compared to pure sumatriptan of 280 nm. These methods provides an effective and less expensive method for measurement of the triptans specially for developing countries.

Keywords: Triptans; 5-HT1-receptor; oxidizing agen; zolmitriptan

Introduction

Triptans are a specific type of serotonin receptor agonists that work by binding to serotonin (5-HT) receptors in the brain, leading to the constriction of blood vessels and the reduction of inflammation associated with migraines [1]. Zolmitriptan, belongs to the triptan family, is utilized for the acute treatment of migraines with or without aura, acting on activating serotonin receptors specifically 5-HT1B/1D [2, 3] Similar to zolmitriptan, sumatriptan is commonly used for the acute treatment of migraines by acting on serotonin receptors [4, 5]. The effectiveness of triptans can vary among individuals, with some experiencing significant relief, while others may have partial or no response [4, 5]. Mild and temporary side effects of sumatriptan and zolmitriptan may include dizziness, drowsiness, fatigue, flushing, sensation of warmth or tingling, and injection site reactions [2, 3]. However, a more serious side effect is serotonin syndrome, which can occur when the body overproduces serotonin[6, 7] . The concurrent use of antidepressants, such as selective serotonin inhibitors and norepinephrine, in combination with migraine medications like triptans, was initially believed to elevate the risk of serotonin syndrome[8]. There are four methods for estimation of triptans; chromatographic, electrochemical, spectrometric, and capillary electrophoretic. Each of them has many limitations such as sensitivity difficulties as obtaining adequate sensitivity for low triptan concentrations is still a hurdle in experimental methods [9]. In addition, matrix interference

due to complex matrices in biological samples leads to matrix effects, which can affect the accuracy of trypton measurements Furthermore[3], ensuring high selectivity and specificity in the presence of coexisting compounds is a challenge in triptan analysis [8]. Inconsistent sample preparation procedures may introduce variability, affecting the reproducibility of triptan measurements [1]. Another concern is the susceptibility of triptans to degradation poses challenges, impacting the stability of these compounds during analysis[6]. In this study, sumatriptan and zolmitriptan were measured in pharmaceutical preparations: tablets, by reacting them with different color-producing reagents for identification and quantitative analysis. The determination of triptans in pharmaceutical formulations involves various analytical techniques, including chromatographic and spectrophotometric methods. Different coupling reagents were utilized to produce colored complexes of drugs with reagents, and then UV-VIS spectrometric analysis was conducted. We tried to develop a spectrophotometric method with coupling reagent to determine the presence and concentration of sumatriptan and zolmitriptan in pharmaceutical preparations that is highly efficient, precise, fast and economical way

Methods

We tried to find the best way to identify and measure triptans concentrations, through a multi-step approach as shown below after processing of the triptan tables and then reacting them with different reagents followed by spectrophotometric measurements

Solubility test

To remove dyes and other binding agents dissolved in water, ten tablets of each medication were crushed and transformed into a powdered form, which was then washed repeatedly with distilled water. Various solvents were tested to assess their solubility, helping to identify the most appropriate solvent for extracting both drugsAs a result, solvents such as 10% NaOH, HCl (1N), toluene, n-butanol, chloroform, ethanol, methanol, ether, and petroleum ether were utilized

Extraction and Separation of Triptan from Medicines

For the extraction of triptan from pharmaceutics 10 g of tablets was weighed, grind into fine powder and added into 25 ml of volumetric flask. 5 ml of chloroform and HCL (1M) was added and mixed it well. Mixture solution was put into separation funnel and shake it for two to five minutes to prevent the creation of emulsions. After that, the two layers were split apart, separated them and recrystallized them by following to measure their respective melting points[10].

Recrystallization of Triptans

About 1.5 g of drug was added into beaker (100 ml) and 35 ml of ethanol was poured with addition of small amount of charcoal and two boiling beads. The beaker was heated on gasoline burner and shaked to help the solution dissolving. After that, hot solution was filter to get rid from charcoal and any other insoluble impurities. To avoid the formation of crystal on filter paper, hot filtering funnel was used and to enhance the speed of filtering, filter paper with folds was used. Allow the filtrate to cool until crystals begin to form (an ice bath can be employed to ensure complete crystal separation from the solvent). Subsequently, the drug crystals are separated by filtration using a Buchner funnel. A filter paper with the same surface area as the bottom of the funnel is positioned in the Buchner funnel, and a small amount of solvent is utilized for rinsing the crystals. The drug crystals are then carefully transferred for drying, either by placing them in an airy location for a day or in a dryer containing a water desiccant like calcium chloride. To assess the impact of impurities, the drug's melting point is measured both before and after the recrystallization process, as the presence of impurities can cause an increase in the melting temperature[11] .

Reaction with Reagents as Coupling Agents

1. Oxidation reaction

For the oxidation reaction of the trepans, 0.5 g of the drug was weighed and transferred into conical flask. After that, 2 ml of KIO3 dropwise and 1 ml of H2SO4 (0.1N) was added into drug solution. After that, 1 ml of potassium permanganate was added gradually over it and incubate at room temperature. The final mixture was analyzed under UV-VIS spectrometer to find the maximum absorption value.

2.Schiff's base procedure

In a round bottom flask of 200 ml, approximately 30 ml of 0.03 mol of propanol, absolute ethanol and three drops of diethyl ether was added and mixed the solvents well. In the mixture, 5 drops of glacial acetic acid were added and mixture was stirred. After that, 2 mol of drug was added and kept the mixture on stirring for complete homogenization of mixture, about an hour till the color of reaction changed. The final solution was removed from magnetic stirrer and left it for 4 hours to form the precipitate and settle down in the bottom. The obtained precipitates were filtered and dried. For UV-Vis spectrometric analysis 0.3 gm. of precipitate was dissolved in an ethanol and few drops of HCl (0.1N) and measure the maximum absorption wavelength[12] .

3.Azotization coupling reaction procedure

A. Azo dyes preparation procedure

For azotization coupling reactions, azo dye preparation method was applied. Therefore, 30 mg of oven dried iron filling and 15 ml of p-nitro phenol was added into 500 ml of round bottom flask. A reflective capacitor was fixed on the beaker, without passing of cooling water. 75 ml of concentrated HCl was added from which, about 15 ml of the acid was poured through the condenser. When the hot mixture was poured into the mixture, the solution start boiling vigorously, and intensified the speed of reaction. By submerging into cold water, the intensity of the reaction can be measured. After that, the mixture was heated again in water bath for 30 to 60 minutes, until the odor of nitrobenzene gone and reaction was stopped by addition of acid in it.

B. Azotisation coupling reactions

For the azotisation coupling reaction, 0.1 g of drug was dissolved into 2 ml of 10% HCl diluted within 5 ml of water and kept the solution at 5 °C. Add few snowflakes to the reaction mixture if necessary to control the temperature. Stir the solution vigorously, and then 2ml of diazonium salts solution was added to separate the crystals. Placed the final solution in an ice bath for 15 minutes in order to settle it down. Filtered the solution by using a Buechner funnel and washed the crystals with water. The final product was measured by UV-VIS spectrometer.

4.Birch of dyes procedure (indirect reactions)

Prepared a solution of 0.1g of drug into 2 ml of 10% diluted HCl in 5 ml of water. After that, 1 g of Bodipy-dye was added and shake the mixture to make solubility of reactant fast. The final mixture was analyzed under UV-VIS spectrophotometer [13].

5. Reaction with chromogenic reagents in basic mediums

For the preparation of chromogenic reagent solution, 0.1 g of drug was dissolved in 2 ml of 10 % HCl diluted with 5 ml of water. Later on, 1ml of NaOH (0.1 N) solution was added with the addition of 0.3 g of phenolphthalein. The final mixture was shaked, until the change in color of the mixture was observed. The mixture solution was analyzed for spectrometric study under UV-VIS spectrometer.

Result and Discussion

1.UV-vis absorbance of the tested drugs

we scanned for the UV-VIS spectrum of Zolmitriptan between 200 to 900 nm of wavelength and the maximum absorbance value at 236 nm of wavelength as indicated in Figures 1A. While for sumatriptan the maximum absorption was at 268 nm (Figure 1B) when the scanning spectrum was done as above.

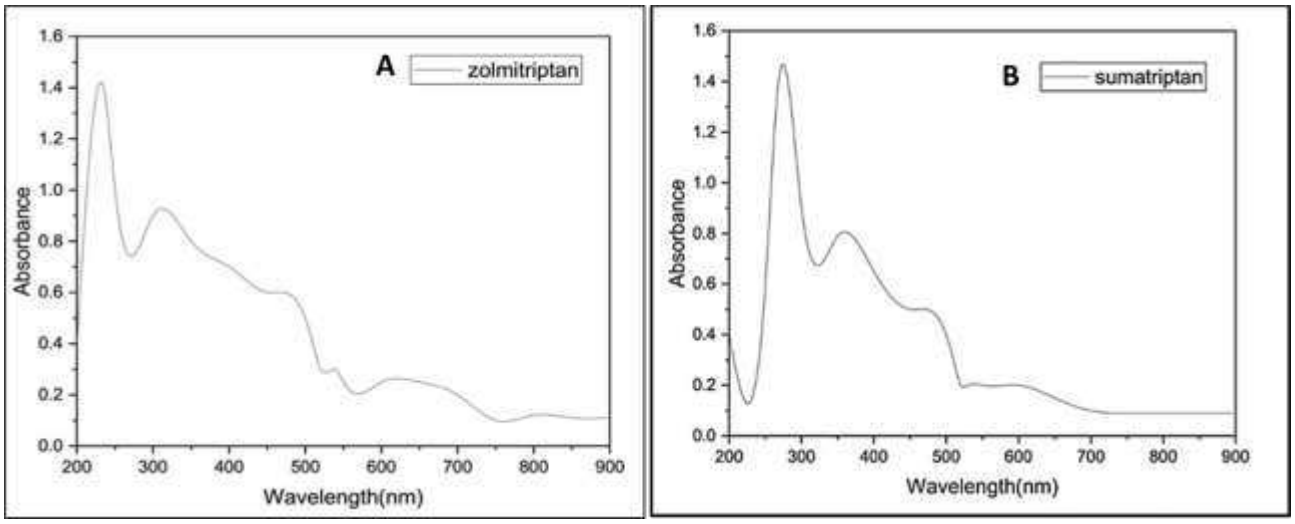

Figure 1: A: UV-VIS absorption spectra of zolmitriptan while B: is UV-VIS absorption spectra of sumatriptan

2.Determination of Drugs Formation of Different Color Products by Organic Reagents

The solubility of both drugs was investigated using a thin layer chromatography (TLC) experiment. A spot appeared on the surface of chromatographical paper which indicate the solubility of the drugs molecules as shown in Figure 2.

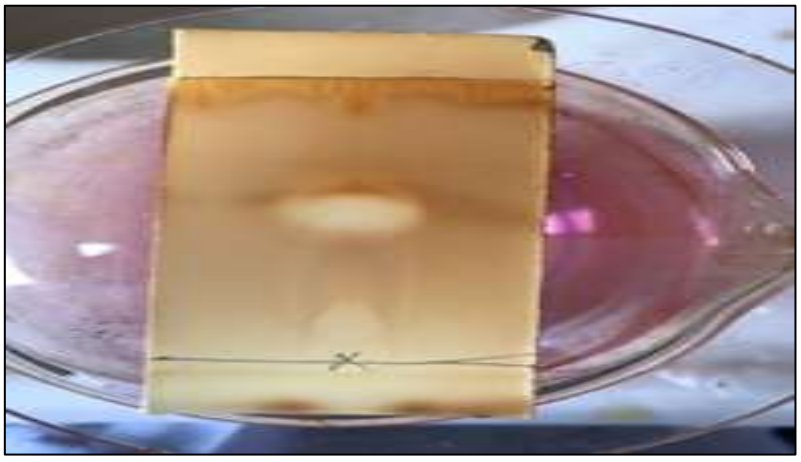

Figure 2:Thin layer chromatography of drugs

3.Determination of Drugs by Formation of Colored Products

For the determination of drugs qualitatively and quantitatively, a series of reactions were conducted following the purification of both medicines. It was observed that, reaction of sumatriptan with Schiff base, oxidizing coupling reagent give blue and yellow colored product. While oxidation reaction and reaction with chromogenic reagents in basic media was observed as light violate and red respectively. In addition, sumatriptan's reaction with Blrch of dyes as an indirect reaction give yellow colored product. Similarly, the zolmitriptan's reaction with Schiff base, Blrch of Dye as indirect reaction give light yellow, while azotization coupling reagents give yellowish blue color as final product. Moreover, the oxidation reaction and reaction of zolmitriptan with chromogenic reagent in basic medium provide light orange and red color respectively. For the determination of drug in pharmaceutics, different method was applied to obtained colored products. The oxidation reaction of both drugs (Figure 2.A and B a) was carried

out in the presence of potassium permanganate (KIO3) as an oxidizing agent. Similarly, an indirect method of Schiff's bases was applied on zolmitriptan and sumatriptan drugs. Schiff bases are compounds that incorporate either an aldehyde or a ketone as their parent molecule. In the study, both drugs were subjected to a reaction with benzaldehyde, resulting in the formation of Schiff base complexes of the drugs [14] . After that absorbance spectra of the complexes of both drugs were studied under UV-VIS spectrometer as shown in Figure Figure 2.A and B.. For determination of drug molecule by producing colored product, azotization method was also studied. The final product formed after following azotization method were analyzed spectrophotometrically and are shown in Figure 2.A and B. The results of reaction of phenolphthalein with zolmitriptan and sumatriptan drugs are given in Figure 2.A and B. UV-VIS spectra of zolmitriptan and its complexes with different coupling reagents are given in Figure 1A, shows that, after reaction of zolmitriptan with Schiff base, azotization, oxidation reaction, reaction with chromogenic reagent in different pH environment and Blrch reaction. The absorption of colored compound was observed at different wavelength values, depending on reaction. It was found that, the resultant product of zol-shc, zol-azo, zol-oxi, zol-chro and zol-blrch give maximum absorbance at 510 nm, 540 nm, 490 nm, 520 nm, 505 nm of wavelength respectively, compare to zolmitriptan at 240 nm. In addition, graphical representation of UV-VIS spectrum of complexes formed after reaction with sumatriptan as shown in Figure 2B. After reaction with different coupling reagents, similar results were observed for suma-shc, suma-azo, suma-oxi, suma-chro and suma-blrch 525 nm, 540nm, 515 nm, 530nm, 520 nm and 480 nm of wavelength respectively compared to pure sumatriptan of 280 nm.

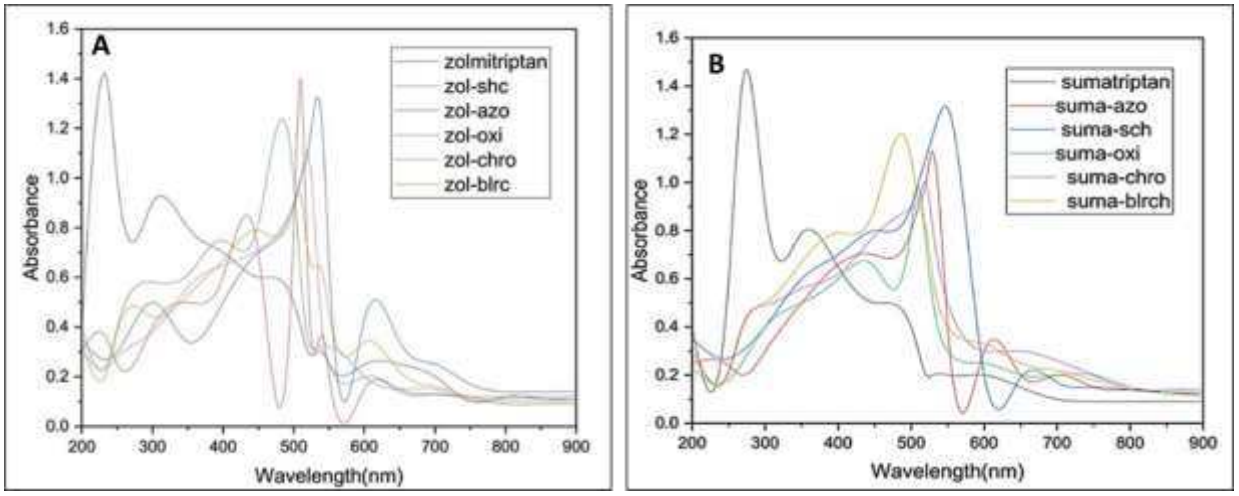

Figure 2: A: UV-VIS absorption spectra of zolmitriptan complexes after reaction with different coupling reagent. B: UV-VIS absorption spectra of sumatriptan complexes after reaction with different coupling reagent. B:

Discussion

Triptans are important drugs for treatment of neurological diseases mainly, migraine[4, 7] . Their measurements in blood and their pharmaceutical formulations is important and essential in medical practice. Many methods have been developed to tackle this issue, each with its own limitations and pitfalls. In this work we tried to develop a technique that is simple, unexpensive and can be applied in laboratory settings with limited resources. This method allows the tablet to be converted into a reactive form that can be used for spectrophotometric measurements. Analysis of the UV-VIS spectra of zolmitriptan and sumatriptan in the wavelength range from 200 to 900 nm revealed distinct absorption peaks Zolmitriptan showed maximum absorption at 236 nm, while sumatriptan showed its peak at 268 nm (Smith et al., 2022). These peaks indicate electrotransitions in drug molecules and provide important information for their detection and characterization in

drug analyzes [15] . The solubility of both compounds was studied by thin layer chromatography (TLC). The visible contrast on the color graph paper indicated the solubility of the drug particles [16] . TLC is a valuable method for preliminary analysis of the conductivity and solubility of synthetic materials in pharmaceutical research [16]. For qualitative and quantitative identification of the drugs, after purification of zolmitriptan and sumatriptan, a series of products were synthesized Reaction of sumatriptan with Schiff base and oxidizing coupling reagents gave blue and yellow products. In addition, oxidation reactions in basic media and reactions with chromogenic reagents produced yellow and light yellow products. Reaction of the compounds with Blrch by indirect synthesis of sumatriptan gave a yellow product. Similarly, indirect reaction of Zolmitriptan with Schiff base and Blrch of Dye gave pale yellow products, while azotization coupling reagents gave yellow-blue final product Also, the oxidation reactions of Zolmitriptan with chromogenic reagents are carried out in basic medium in, and reactions caused by pale orange-redutpads. In the pharmaceutical industry, various techniques have been used to obtain colored products for the detection of chemical molecules. The oxidation reactions of both compounds were carried out in the presence of potassium permanganate (KIO3) as an oxidizing agent. An indirect method involving a Schiff base complex was used to prepare Schiff base complexes for both compounds. The absorption spectra of these complexes were studied under a UV-VIS spectrometer [14] . In addition, using azotization techniques, the final products were analyzed spectrophotometrically The UV-VIS spectra of Zolmitriptan with different coupling reagents and surroundings exhibited absorption peaks at different wavelength values for Zolmitriptan , Zol-Azo, Zol-Oxy, Zol Cro, and Zol-Blch exhibited maximum absorption at 510 nm, 540 nm, 490 nm, 520 nm, and 505 nm, respectively, for comparison purposes from pure zolmitriptan occurred around 240 nm a. Similarly, the UV-VIS spectrum of the complexes formed after the reactions with sumatriptan showed absorption peaks at 525 nm, 540 nm, 515 nm, and 530 nm for suma-shak, suma-azo, suma-oxy, suma-1. cro, and suma-blch , as well as 520 nm, respectively, at 280 nm compared to pure sumatriptan.. These findings provide a comprehensive understanding of the pharmacological properties and behaviors of zolmitriptan and sumatriptan under various experimental conditions, and provide valuable insights for drug development and quality control [17]. In summary, the analysis of zolmitriptan and sumatriptan using cost-effective methods such as UV-VIS spectroscopy and thin layer chromatography provided valuable insights into their chemical properties UV-VIS spectra revealed distinct absorption peaks at 236 nm for zolmitriptan and 268 nm for sumatriptan ANI, . The solubility of both compounds was confirmed by thin layer spectra that contributed to rapid detection, highlighting the simplicity and cost-effectiveness of this method.

Conclusion

Different procedures for qualitative and quantitative analyzes resulted in a variety of colors, demonstrating the versatility of these cost-effective methods for UV-VIS spectroscopy, thin layer chromatography, and other chemical syntheses - Provide a basis for quality, contributing to cost-effective drug development and management, especially in resource-limited environments

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