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Validation and Determination of Tamsulosin Hydrochloride Residue in Production Line Equipment by HPLC after In-tube Solid Phase Microextraction

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Abstract

Ensuring about the cleanliness of the product line is a major approach on famous pharmaceutical companies. The aim of this study is validation of in-tube SPME (IT-SPME) method coupled with HPLC-UV for microextraction and determination of tamsulosin hydrochloride (TAM) residue from swab samples of pharmaceutical production lines. The inner surface of stainless steel tube which is proposed as device for TAM extraction was coated by Polypyrrole (PPY) via chemical polymerization reaction. After five cycles of polymerization, the tube was coated with acceptable stability that can overcome five extractions. Three practical parameters such the effect of pH, ionic strength and extraction cycle were optimized. The maximum extraction yield was achieved when no salt added, pH was adjusted at 8 and extraction cycle was chosen at 11 times. Then a mixture of sodium perchlorate buffer (pH=2) and acetonitrile (35:65) was utilized as desorption solvent. Linear dynamic range (LDR), limit of detection (LOD) and relative standard deviation (RSD) of proposed method were calculated between 5-2500 ng mL^{-1}, 1.62 ng mL^{-1} and 1.23%, respectively. Moreover, the proposed method was compared with standard method of TAM residue determination from swab samples of pharmaceutical production lines. The results revealed that the proposed method can be utilized as an acceptable method for isolation and determination of TAM from swabbing samples.

Keywords: Tamsulosin hydrochloride; Swab sampling; In-tube SPME; Polypyrrole.

Introduction

The prostate is a male genital and walnut size gland which is located after the bladder. Benign prostatic hyperplasia (BPH) is the most frequent prostatic disorder that occurs in aging, and it refers to the noncancerous growth of the prostate. Almost 75% of men over the age of 70 suffer from BPH. Its symptoms are nocturia, intermittent urinary retention, and ultimately renal failure. The first treatment for BPH is

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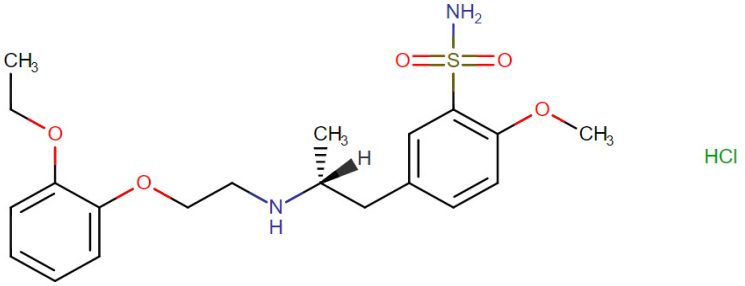
considered oral drug therapy. It is believed that tamsulosin hydrochloride (TAM) can be used to treat this condition. TAM is a highly selective α1A-adrenoreceptor antagonist. Its physical and chemical properties are presented in Table 1 (1-3). It is an official drug in the United States Pharmacopeia (USP) and the British Pharmacopoeia (BP) with potentiometric titration described for its assay in bulk powder. The USP also described high performance liquid chromatography (HPLC) for TAM assay in capsules. A survey of the literature revealed that several analytical methods such as spectrophotometric (4), spectrofluorimetric (5), HPLC (6-8), capillary electrophoresis (CE) (9), LC-MS (10) and electrochemical (11) methods have been reported for the determination of TAM in various matrixes. A wide diverse of analytical methods for this purpose were summarized in the review article by Shrivastava and coworkers (12). Furthermore, the concentration of degradation products of TAM was determined by HPLC (13) and HPTLC (14). It is believed that an extraction process as a part of sample preparation is essential in the determination of analyte in the trace level (Table 1).

Sample preparation techniques with miniaturized approaches have attracted substantial attention. An innovative sampling technique developed by Arthur and Pawliszyn that is called SPME. It is a solvent less and equilibrium-based technique that also uses a small amount of extraction phase, while, providing accurate and reproducible results at the same time (15). Therefore, it has been extensively used in environmental, medicine, food, and biological analyses. Moreover, further treatment of the sample after enrichment is unnecessary when using SPME, which guarantees the precision of the method and easy automation of the whole manipulation (16-19). IT-SPME coupled to HPLC was first introduced by Eisert and Pawliszyn in 1997, and it utilized an inner surface coated open tubular fused-silica capillary as the extraction phase (20, 21). IT-SPME is an efficient sample preparation technique that usually employs either a coated, packed or a monolithic capillary tube containing a proper sorbent which extracts and concentrates target analytes from aqueous matrixes (22). It can be easily automated and coupled to HPLC. Since the volume of extraction sorbent in IT-SPME is generally small, developing sorbent with high extraction efficiency is always an attractive task. Furthermore, many coated format of extraction capillaries (or tubes) have been employed in the extraction system (23-25). Commercial extraction phases used for IT-SPME do not show high extraction abilities for ionic compounds, especially acidic ones and polar compounds (15, 26-30). In IT-SPME, some conductive polymers, such as polypyrrole and polyaniline, were coated on the inner surface of the stainless steel tube and employed as the extraction medium (31, 32). Intrinsically conducting polymers with conjugated double bonds have attracted much attention as advanced materials because of their potential applications like corrosion-resistant coatings, ion exchangers, materials for separation, biosensors and chemical sensors (33, 34). Among those conducting polymers, polypyrrole (PPY) and its derivatives have become one of the most widely studied coatings due to

Table 1. Physical and chemical properties of TAM

Property	
Synonyms	Tamsulosin hydrochloride; Tamsulosin HCl; Flomax; Omnic
Chemical structure	
Molecular formula	$C_{20}H_{29}ClN_2O_5S$
Molecular weight	445 g mol^{-1}
Form	White powder
Water solubility	215.9 mg L^{-1} at 25 °C
Log p	3.05
pK_a (strongest acidic)	9.93
pK_a (strongest basic)	9.28

their facile polymerization from organic or aqueous media through electrochemical or chemical methods and higher conductivity than many other polymers (35, 36). Recently, Zakerian et al. could coat successfully PPY on the inner surface of a fused silica capillary (37). Due to the inherent multifunctional properties of PPY, such as acid-base interactions, ion exchange, and hydrogen bonding (20, 38, 39), the PPY coated capillary has demonstrated higher extraction efficiency toward polar compounds, aromatic compounds and anionic species as compared with most of the currently used commercial capillaries in IT-SPME (20, 33, 40, 41). Two reasons for the rapid and easy extraction of aromatic and ring compounds by polypyrrole are π–π and hydrophobic interactions. There are a wide range of pharmaceutical materials which were extracted by IT-SPME like amitriptyline, imipramine, chlorpromazine, thebaine, indomethacin, naproxen, oxazepam and lorazepam.

Pharmaceutical industries follow very high and stringent standards, because their products are directly related to human health. Along with all these standards, the cleaning of the equipment of production lines follows a certain standard. The importance of this is due to the fact that a production line may be used to produce several products, so the transfer of possible contaminants as active ingredients, detergents and microorganisms from each product to the next can be the greatest threat to the quality of pharmaceuticals. According to the 1993 FDA guide (42) swabbing is the acceptable method for validation of production line cleaning in pharmaceutical industries. According to the guidelines, a standard swabbing must offer minimum extractable interferences, ultra-low particles, solvent compatibility, high active pharmaceutical ingredient residue absorbance during sampling and low active pharmaceutical ingredient residue retention during sample preparation.

In this study, polypyrrole was selected due to its high stability, desirable and increased conductivity and environmental friendly. In addition, its stable polymer film is easily coated on metal wires. However, due to the mentioned advantages of polypyrrole, this polymer can be used to extract the analyte. The most important purpose of this paper is to investigate the application of PPY coated tube as IT-SPME device for extraction and determination of tamsulosin hydrochloride from production lines by the swab sampling method followed by HPLC. At the end, the mentioned method was compared by a reference method for extraction and determination on TAM from swab. This study can open new windows on using precise, fast, environmental friendly, safe and useful method to determine the concentration of residue drug in the product line.

Materials and Methods

1. Chemicals and standards

Pyrrole (98%), isopropyl alcohol, perchloric acid and Iron (III) chloride ($FeCl_3 \cdot 6H_2O$) were purchased from Merck KGaA (Darmstadt, Germany) and pyrrole was distilled before utilization. Distilled pyrrole was protected from the light exposure and was kept at 4 °C. HPLC grade methanol (MeOH) and acetonitrile (ACN) were obtained from DAEJUNG Chemicals (South Korea). TAM was gifted from DaruPakhsh chemical and pharmaceutical Co. (Iran). Other solvents and reagents were bought from Fluka AG (Switzerland). In order to prepare the weekly stock solutions of TAM (1000 μg mL^{-1}), an appropriate amount of TAM was dissolved in minimum volumes of acetonitrile and then this solution was transfer to 1000 mL volumetric flasks of redistilled water. The stock solution was stored at 4 ℃. The test solutions were prepared daily.

2. Apparatus

High performance liquid chromatography instrument model 1525 (Waters, USA) equipped with an isocratic pump, 20 μL sample loop and UV detector was utilized to determine TAM concentration. A homemade pump was used for monomer and oxidant solution passing through the tube. To adjust pH of sample, a pH meter (Metrohm, 691) was utilized to measure pH of samples. The sorbent morphology was investigated by scanning electron microscopy (EM208, Philips). An ultrasonic bath (Branson 3510, Branson Ultrasonics Corp., USA) was applied to desorb analyte from the swabs.

3. Chromatographic conditions for TAM separation and determination

Separations were performed at 40 ºC on an YMC C-18 column (150×4.6 mm, 5μm). Mobile phase consisted of a mixture of sodium perchlorate buffer (pH=2) and acetonitrile (35:65) was applied, and detection wavelength was set at 225 nm.

4. Preparation of IT-SPME sorbent

To obtain a piece of stainless steel tube (300 mm length, 0.25 mm I.D), some steps are essential. They are presented briefly here.

In order to create a suitable substrate for coating of pyrrole on the inner surface of tube, an oxidant ferric chloride solution (1M) was passed by homemade pump through the tube.

Then pyrrole solution in isopropyl alcohol (10% W/W) was passed, and this step was repeated for 5 times.

After completing the polymer preparation procedure, the tube was dipped into methanol.

At the end, nitrogen gas was used to dry the tube.

5. Analytical procedure

The foundation of SPME is based on sorption phenomena. Here the proposed tube was mounted in HPLC instead of loop to make an online IT-SPME. The optimization experiments were carried out on the tube. The pH of the sample was adjusted at desire values and some salts were added. The sample was introduced to the tube via draw-inject process followed by eluting with mobile phase as desorption solvent.

Results and Discussion

1. Preparation of PPY-tube and its morphological study

To achieve the best result, it seems necessary to coat a uniform, homogenous and stable layer at the inner surface of the proposed tube. PPY-tube can be obtained by passing a solution of pyrrole and oxidant through the stainless steel tube, and this step was repeated several times. Results show that passing the polymerization reagents lower than 5 cycles produces an unstable PPY packing in the tube, which was bled from the tube during elution. While, the proposed tube was closed after passing the polymerization reagents more than 5 cycles. So, five cycles polymerization was selected as the best result for preparation of PPY-tube. The proposed tube was cut, and it was investigated by electron scanning microscopy (SEM). Figure 1 represents SEM images of PPY-tube. Figure 1(A) shows the cross section of PPY-tube and indicates the polymer was distributed perfectly, and chemical coating procedure was successful. Fig. 1(B) depicts the same SEM image with 11-fold magnification. The porous structure of the coated layer was proved by this micrograph. Thermal stability is not important in this study because PPY-tube was used in HPLC system.

2. Optimization of factors affecting IT-SPME of TAM

To achieve the highest efficiency of TAM extraction by IT-SPME some practical parameters were investigated and optimized. The effect of number of extraction cycles, pH and ionic strength were the parameters which were studied. The optimization process was accomplished in triplicate.

2.1. Selection of the best extraction cycles: It is well known that extraction efficiency is directly depending on contact time between sample and extracting phase. In IT-SPME, number of extraction cycles through the tube is an appropriate alternative parameter for investigating extraction time. 20 µL of sample was drawn at the flow rate of 100 µL min^{-1} to PPY-tube from sample vial. In order to select the optimum number of extraction cycles, sample solution was passed through the tube for 1-14 cycles. Results show that after 11 cycles, the amount of extracted analyte reaches the equilibrium state (Figure 2). This trend can be due to the fact that at the beginning and up to 11 cycles, the number of active sites related to the adsorbent is high, and the TAM is rapidly adsorbed on the PPY-tube. After 11 cycles, due to the saturation of the adsorbent, which is caused by over-crowding of the TAM, the trend is constant and the rate of adsorption/desorption seems constant. So, 11 cycles were selected for further studies.

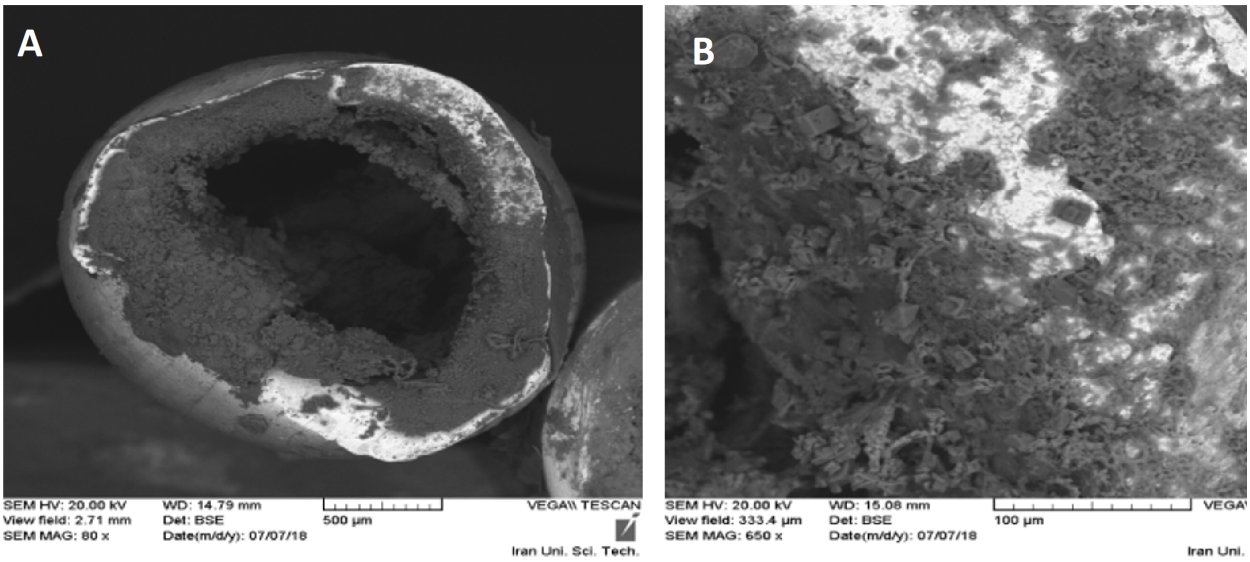


Figure 1. SEM micrographs from cross section of PPY-tube with magnification of (A) 60× and (B) 650×

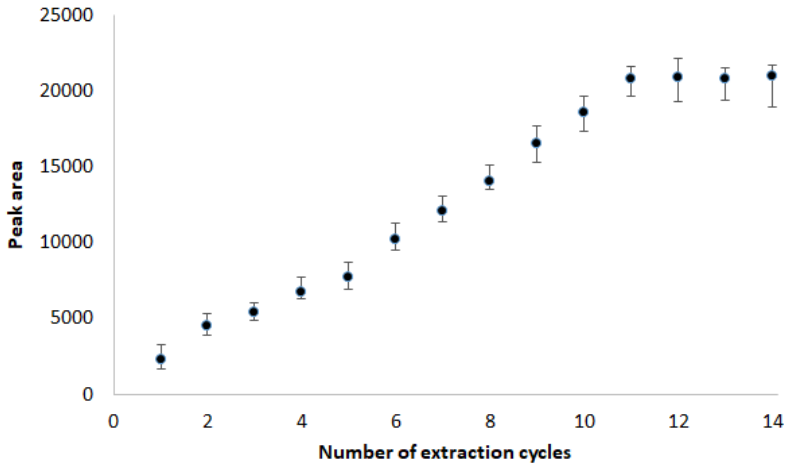


Figure 2. Effect of extraction cycles on the amount of TAM extraction (extraction conditions: TAM concentration, 200 ng mL-1; sample volume, 20 µL; sample pH, 8; No Salt)

The extraction mechanism of most analytes by porous coatings is based on Langmuir isotherm, which is related to adsorption process. It means that the number of active sites in the adsorption phenomenon is limited. In the other words, no more analyte is adsorbed when all active sites are occupied, and it proves that the adsorption process is competitive (39). Using the results of the optimization process of extraction cycles, the extraction mechanism can be logically inferred. As can be seen in Figure 2, when the number of unoccupied sites in the low extraction cycles is high, the competition for occupying active surface sites is low, and it gradually increases until after 11 extraction cycles the yield reaches the highest value and competition. According to the contents and the theory of Langmuir isotherm, the process of TAM extraction by PPY-tube SPME is probably based on adsorption and following the Langmuir isotherm. Several other articles have studied the type of mechanism (43-45).

2.2. Effect of pH: pH shows a great effect on the extraction of polar drugs. Theoretically, by adjusting the sample pH, an increase in extraction yield occurs due to the decrease in the solubility of the analyte in water. In this case, the coated layer (PPY) is deprotonated at pH 9-11 and at lower pH it is in protonated form (positively charged chain) (46). Effect of pH on extraction of TAM by IT-SPME which was coated by PPY was investigated over the range of 1-11. Sample pH was adjusted by 0.1 M NaOH or HCl. Due to the chemical nature of TAM as a weak base (pka=9.28) at pH values lower than 9, both of the TAM and PPY chain were in protonated form. Since the analyte and adsorbent repel each other electrostatically, the extraction efficiency of the TAM by PPY is in the lower value. At higher pH (>9) both of them are almost neutral, and this condition is favorite for extraction. Figure 3 depicts that increasing peak areas of TAM reaches to a constant level at pH values higher than 8, therefore the pH=8 was selected as the best pH for extraction of TAM.

2.3. Effect of ionic strength: Generally, the extraction efficiency of the analytes into a stationary phase in SPME can be increased by changing the pH and salt concentration of the sample solution. Salt dissolution can influence on ionic strength, and therefore it can change the extraction efficiency. So, effect of different amounts of NaCl as an inorganic salt was evaluated in this study. Different amounts of sodium chloride (0, 0.1, 0.5 and 1 g L^{-1}) were added to the sample solution and extractions were carried out. As can be seen from Figure 4, salt addition has significant adverse effect on extraction efficiency in the concentration range studied. Salt addition can affect on the viscosity of sample solution and by increasing the viscosity the extraction yield decline. Moreover, this trend can be seen because of enhanced dissolving of TAM in the sample solution. Thus, further extractions were performed without salt addition.

2.4. Sorbent efficiency study: Stability and performance of the proposed sorbent (PPY which is coated in the inner surface of tube) are important characteristic parameters. For this purpose, multiple extractions were performed using one PPY-tube. Figure 5 shows that after 5 experiments, extraction efficiency decreases to 7%, 15% and 40% loss of performance for 6^{th}, 7^{th} and 8^{th} extractions, respectively.

2.4. Analysis of real samples: In order to evaluate feasibility of the presented method for extraction and determination of TAM, some real samples (swab sample

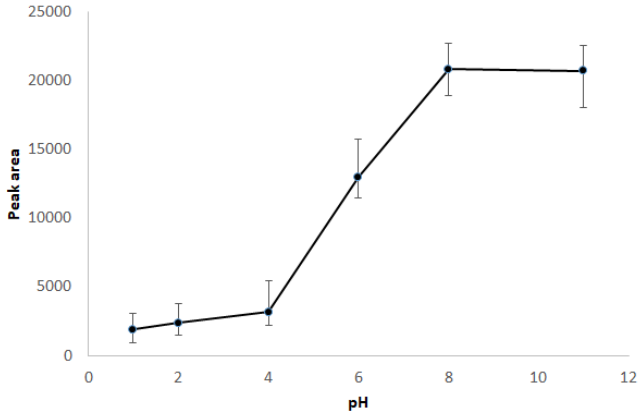


Figure 3. Effect of pH on TAM extraction efficiency (extraction conditions: TAM concentration, 200 ng mL-1; sample volume, 20 µL; extraction cycles, 11; No Salt)

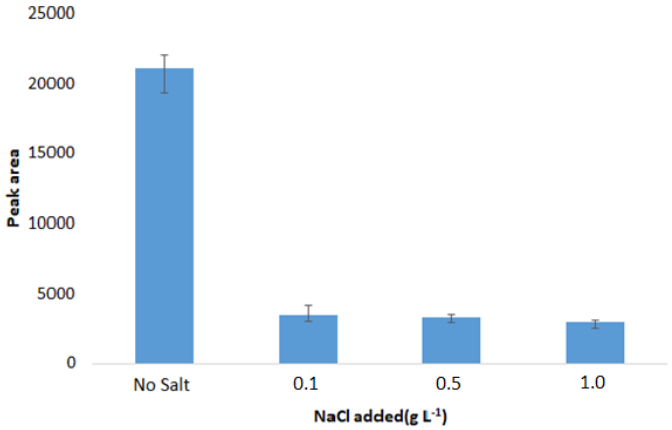


Figure 4. Effect of salt addition on TAM extraction efficiency (extraction conditions: TAM concentration, 200 ng mL-1; sample volume, 20 µL; extraction cycles, 11; pH, 8)

and washing water sample) were analyzed. 100 cm^2 of sampling surface which is accessible was wiped with cotton swab. After completely swabbing the surface, the cotton swab was transferred to the 5 mL vial and adsorbed drug residue was desorbed by 2 mL of mobile phase via sonication. For inaccessible surfaces, washing water was sampled for TAM residue analysis.

IT-SPME was performed on a 200 µL of sample in the optimal conditions. Real samples analysis showed that no detectable amount of TAM was present. Three different concentrations of TAM (100, 200 and 300 ng mL^{-1}) were utilized to study the matrix effect. The recoveries of TAM following by microextraction and chromatographic determination for swab sampling and washing water were calculated to be 89.40% and 94.10%. Recovery data demonstrates that the proposed method had no significant matrix effect on determination of TAM in real samples. Typical chromatogram regarding spiked swab sample are shown in Figure 6.

3.3. Validation data

Validation of pharmaceutical processes is the most significant parameter of current good manufacturing practice cGMP. Process validation is one of the requirement of a quality control system. Validation is an important part in ensuring that this goal is achieved. Figures of merit for IT-SPME of TAM which is achieved under optimum conditions (extraction cycles=11, pH=8 and no salt added) are presented in Table 1. Repeatability of the proposed method was examined by five replicated analyses of 20 µL TAM at 200 ng mL^{-1} level using a PPY packed tube. Results revealed that RSD of the method was 1.23% which

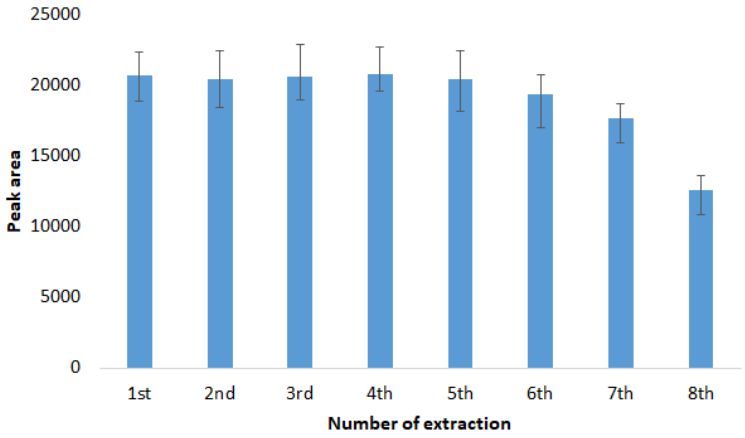


Figure 5. Performance study of the proposed IT-SPME after multiple extractions

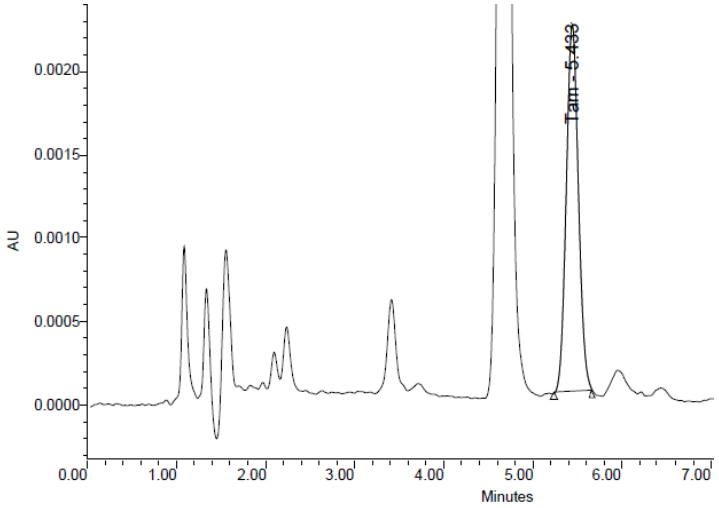


Figure 6. Chromatogram of spiked swab solution (100 ng mL^{-1} of TAM)

confirmed perfect repeatability of the proposed method. The TAM calibration graph was linear in the concentration range of 5–2500 ng mL^{-1} with satisfactory coefficient of determination (R2=0.999). Limit of detection (LOD) based on signal-to-noise ratio of 3:1 was calculated 1.62 ng mL^{-1}. At the end, the total analysis time was obtained 16 min.

In this study, the proposed method was compared with liquid-liquid extraction (LLE) method as a reference way for determination of TAM. In order to utilize LLE, 250 µL of sodium carbonate (1M) was added into 1 mL of sample solution containing 200 ng mL^{-1} of TAM. Then, 3 mL solvent mixture (Hexane: Ethyl acetate,2:1) was added, and this mixture agitated and centrifuged for 1 and 5 min with 2500 RPM, respectively. The organic phase was evaporated to dryness in a 40 ˚C water bath. Next, 200 µL of a mixture of methanol, water and formic acid (80:20:1, v/v/v) was utilized to reconstitute and finally 20 µL aliquot was injected (47-49). LDR of LLE method was obtained in the range of 9-180 ng mL^{-1} with coefficient of determination 0.987. On the other hand, repeatability was achieved less than 10% and total time analysis was obtained 25 min. Moreover, quantitative characteristics of the proposed method such as linear dynamic range (LDR), its correlation coefficient and detection limit of target compound are listed in Table 2.

According to the obtained data from the proposed and reference method, a comprehensive comparison can be used for these two methods. The SPME method has the following advantages:

1) The proposed method has less analysis time.
2) The LDR in the SPME is much better.
3) The RSD of the SPME is much higher than the

Table 2. Analytical figures of merit of the extraction of TAM

Method	LDR (ng mL^{-1})	LOD (ng mL^{-1})	RSD (%)	Total analysis time (min)
IT-SPME	5-2500	1.62	1.23	16
LLE	9-180	0.43	<10	25

standard method.

4) In traditional methods, the use of organic solvents is high and therefore they are harmful to the environment and health.

5) The SPME method seems to be economically viable because it is used several times.

6) The proposed method is capable of coupling with HPLC.

According to the mentioned points, the SPME method is superior to the standard method and can be used as an effective method.

Conclusion

One of the vital challenges in pharmaceutical industries is the ensuring about clean product line. The aim of this project is the study of PPY-IT-SPME efficiency in TAM isolation and its optimization process. IT-SPME was utilized instead of loop, and it was coupled to HPLC-UV to achieve an online-extraction tool. Moreover, three important factors like the number of extraction, pH and ionic strength were optimized. The obtained results represent that when the conditions were kept at 11 extraction cycles, pH=8 and no salt added to the sample solution, the best results can be obtained. The figures of merit revealed that the proposed method has a perfect repeatability, precision and accuracy. By comparing the proposed and standard method, it is clear that IT-SPME has some advantages rather LLE, and it can be accounted as an effective route to determine the residual concentration of TAM in sample solution and accounted as the reference method for TAM detection in product line cleaning.

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