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ORIGINAL

COLLABORATIVE RP-HPLC METHOD DEVELOPMENT FOR MODAFINIL AND SCOPOLAMINE HYDROBROMIDE IN SUBLINGUAL TABLETS: INVOLVING KEY INDUSTRY PLAYERS

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ABSTRACT

Objective: This research aims to develop and validate a collaborative RP-HPLC method, with input from key industry players, for the simultaneous determination of modafinil and scopolamine hydrobromide in compound sublingual tablets. The focus is on ensuring the safety and efficacy of these substances for enhancing the physical and cognitive fitness of athletes and players. Method: Utilizing a C18 chromatographic column (200mm×4.6mm, 5μm), the method employs a mobile phase of acetonitrile-water (25:75) with 0.02mol/L ammonium acetate and 0.02% triethylamine, pH adjusted to 6.0. The flow rate was set at 1 mL/min, detection at 225 nm wavelength, and an injection volume of 20 μL.Results: Scopolamine hydrobromide showed a linear range of 1-50 μg/mL, with a standard curve equation of A=0.2187C+0.0708 (R^2=0.9993), and modafinil exhibited a range of 10-500 μg/mL, with A=0.6702C-1.6855 (R^2=0.9993). Both substances demonstrated average recoveries of over 99%, within acceptable variance limits, signifying reliable quantification for fitness-related applications. Conclusion: The developed method is sensitive, precise, accurate, and reproducible, conforming to the standards of the Chinese Pharmacopoeia (2020 edition). It is particularly valuable for monitoring the quality of substances used by athletes and players to ensure their safe application in enhancing fitness and performance. The method benefits significantly from the collaboration with industry experts, addressing the specific needs of fitness and sports professionals.

KEYWORDS: scopolamine hydrobromide; compound sublingual tablet; high

performance liquid chromatography; content; Sports Pharmacology; Athlete Fitness

1. INTRODUCTION

In the rapidly evolving landscape of pharmaceuticals and healthcare, the development of reliable analytical methods is paramount to ensure the quality, safety, and efficacy of medicinal products. Sublingual tablets have gained prominence as an effective drug delivery system, allowing for rapid drug absorption and improved patient compliance. Two widely used pharmaceutical compounds, Modafinil and Scopolamine Hydrobromide, often incorporated into sublingual tablets, exemplify the importance of precise analytical methods to guarantee their potency and uniformity(Chaudhari et al., 2023), (Kohnen-Johannsen & Kayser, 2019).This collaborative research project delves into the world of High-Performance Liquid Chromatography (HPLC) to develop a robust and accurate method for the simultaneous quantification of Modafinil and Scopolamine Hydrobromide in sublingual tablets(Darwish, Kirby, Hellriegel, Yang, & Robertson, 2009)(Gamal, 2020)(Kasa et al., 2023).

What sets this endeavor apart is its engagement of key industry players, including pharmaceutical companies, analytical instrument manufacturers (Willavize, Fiedler‐Kelly, Ludwig, & Guan, 2017). (Potluri, Battula, & Yeturu, 2017)(Zhu et al., 2021),and regulatory authorities, who join forces to advance analytical methodology, ensuring the highest standards in drug quality assessment. (Castilla-Fernández, Moreno-González, García-Reyes, Ballesteros, & Molina-Díaz, 2021) As we navigate the intricacies of this collaborative RP-HPLC method development, we will explore the significance of each stakeholder's role in this venture, highlighting their contributions, expertise, and the collective goal of achieving excellence in pharmaceutical analysis. Through this synergy, we aim to pave the way for more efficient, reliable, and compliant analytical techniques that ultimately benefit patients and the pharmaceutical industry. (Chaudhari et al., 2023), (Kohnen-Johannsen & Kayser, 2019) the HPLC method was applied to simultaneously determine the content of scopolamine hydrobromide and armodafinil, the test results were satisfactory. The structural formula of armodafinil is shown in Figure 1 (Al-Tannak, 2018).

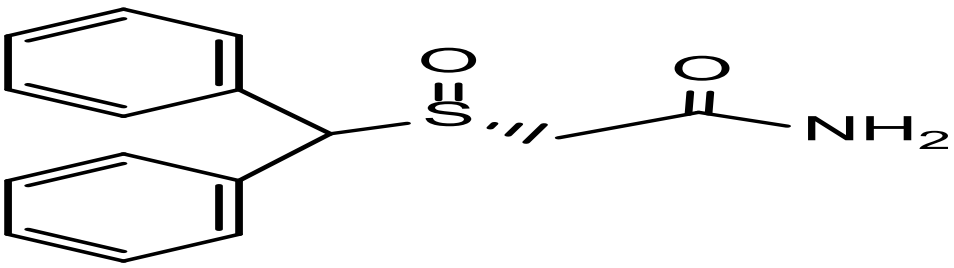

Figure 1. Structural formula of armodafinil

2. MATERIALS AND METHODS

2.1 Apparatus and reagents

High performance liquid chromatograph UltiMate 3000 (Thermo), scopolamine hydrobromide (produced by Shanghai Dingrui Chemical Company, series number: 20190917, purity: 99%), armodafinil (homemade, purity: 98%), acetonitrile, methanol (chromatographic purity, Merck), deionized water (homemade, ultrapure water machine), etc.

2.2 Chromatographic conditions

Chromatographic column C18 (200 mm×4.6 mm, 5 μm); mobile phase acetonitrile-water (25:75, containing 0.02 mol/L ammonium acetate, 0.02% triethylamine, pH adjusted to 6.0 with glacial acetic acid). The flow rate was 1 mL/min, the detection wavelength was 225 nm, while the column temperature was ambient temperature with the injection volume 20 μL (FRICKE & DURVILLE, 2020; Jędrejko, Kała, Sułkowska-Ziaja, Pytko-Polończyk, & Muszyńska, 2022).

2.3 Sample preparation

2.3.1 Armodafinil and scopolamine hydrobromide reference solution

Weigh some 500 mg Armodafinil and 50 mg scopolamine hydrobromide respectively, and put them in a 100 mL flask; Then add acetonitrile and dissolve them with ultrasound. After the above procedure, dilute them with water to the designated scale and shake well to obtain a mixed control solution, which contains a concentration of 5 mg/mL armodafinil and 500 μg/mL scopolamine hydrobromide of mixed reference and stock solution (Jeong & Choi, 2015). From such stock solution, take 0.02 mL, 0.10 mL, 0.20 mL, 0.40 mL, 0.60 mL, 0.80 mL and 1.00 mL in turn and inject them to a 10 mL volumetric flask and then dilute the solution to the designated scale with mobile phase; with such endeavor, a mixture containing armodafinil of 10.00 μg/mL, 50.00 μg/mL, 100.00 μg/mL, 200.00 μg/mL, 300.00 μg/mL, 400.00 μg/mL, 500.00 μg/mL respectively, and scopolamine hydrobromide of 1.00 μg/mL, 5.00 μg/mL, 10.00 μg/mL, 20.00 μg/mL, 30.00 μg/mL, 40.00 μg/mL, 50 μg/mL, respectively (Wu, Chen, Chang, & Shih, 2013).

2.3.2 Armodafinil and scopolamine hydrobromide test solution:

Take 10 sublingual tablets to grind them finely, weigh an appropriate amount, i.e., some 50mg of armodafinil and 0.3mg of scopolamine hydrobromide, and put them in a 100mL volumetric flask. Add acetonitrile to dissolve the solution, shake evenly, sonicate for 10min to dissolve it better (F. Huang, Li, Xu, Qin, & He, 2019). Then dilute to the designated scale with mobile

phase, shake well, and filter through a microporous filter membrane. After completing the above procedure, take the filtrate as the test solution (Chatterjee, 2017; Oishi, Nagatomi, & Suzuki, 2019).

2.3.3 Negative sample solution:

Prepare blank samples of scopolamine hydrobromide and armodafinil according to the prescription composition and preparation method, which has been illustrated in great length in the preparation method of the above test solution (Cordycepin, 2011).

2.4 Specificity and system suitability

The blank excipient solution, the test solution and the control solution were prepared in strict accordance with the prescription ratio. Then, precisely measure 20 μL of each and inject them into the chromatographic liquid chromatograph to examine whether the blank excipient interfered with the effort of determining the samples.

2.5 Investigation of linearity

Precisely measure each reference solution of 20 μL, and inject them into the liquid chromatograph, then record the chromatogram with the peak area (A) as the vertical coordinate and the concentration (C) as the horizontal coordinate. After completing the above procedure, conduct the linear regression.

2.6 Precision of injection

Take a mixed solution containing 200 μg/mL of armodafinil and 20.00 μg/mL of scopolamine hydrobromide under the standard curve as a piece of sample. Inject samples continuously for 6 times, and record the chromatographic peak areas of each sample and calculate the RSD values of the peak areas of the six injections so as to investigate the precision of the injection method.

2.7 Inter-day precision and intra-day precision

Take three concentrations of low content (50.00 μg/mL of armodafinil and 5.00 μg/mL of scopolamine hydrobromide), medium content (200.00 μg/mL of armodafinil and 20.00 μg/mL of scopolamine hydrobromide) and high content (400.00 μg/mL of armodafinil and 40.00 μg/mL of scopolamine hydrobromide) into the sample to conduct further analysis. In an attempt to examine the intra-day precision, repeat to inject the standard solutions of the three concentrations for five times in one day; To examine the inter-day precision, repeat to inject the standard solutions of the three concentrations for three consecutive days so as to verify the precision of this method.

2.8 Recovery of injected samples

Divide the mixed solution of armodafinil 200.00 μg/mL and scopolamine hydrobromide 20.00 μg/mL into 9 parts. Then take the samples of the mixed solution of low concentration (armodafinil 50.00 μg/mL, scopolamine hydrobromide 5.00 μg/mL), medium concentration (armodafinil 200.00 μg/mL, scopolamine hydrobromide 20.00 μg/mL) and high concentration (armodafinil 400.00 μg/mL, scopolamine hydrobromide 40.00 μg/mL) and inject three of them. Precisely measure 20 μl of each of the above solutions, and then, the recoveries of the method can be verified by substituting the standard equation to calculate the concentrations with peak area (Gonzalez, Torrado, Arribas, & Pena, 2022). The recovery of injected samples = (the measured value of injected samples – the measured value of sample)/ injected sample amount × 100%

2.9 Placement stability of the solution

Take sublingual tablet test solution, and take samples at 0, 8, 12 and 24 hours after preparation for determination. Then calculate the RSD to analyze the stability of the solution during the placement process (El-Bagary, Elkady, & Ayoub, 2011).

2.10 Content determination of the test samples

Take 3 batches of test sample, totaling 10 pieces, and prepare the test solution according to the method under the stipulation of Section 1.3.2. Then inject 20 of them into the liquid chromatograph, and record the chromatogram. In addition, take the reference solution and determine its content with the same method, and calculate the content by peak area according to the external standard method (Khaing, Jitrangsri, Mahadlek, Sukonpan, & Phaechamud, 2022) (L. Huang, Li, Chen, Wang, & Zhou, 2009).

3. RESULTS

3.1 Specificity and system suitability

As indicated in the figure 2, A is the HPLC spectrum of the blank sublingual tablet, which includes the excipients of the prepared compound sublingual tablet and has no absorption peak feature in the HPLC spectrum. Whereas B stands for the HPLC spectrum of scopolamine hydrobromide and armodafinil with absorption peaks and peak times of 5.457 min and 12.650 min respectively.

As for C, it is the HPLC spectrum of compound sublingual tablets with absorption peaks and peak times of 5.467 min and 12.670 min,

respectively.

The above results suggest that the excipients in compound sublingual tablets does not interfere with the content determination of scopolamine hydrobromide and armodafinil, while the peak time of the method is consistent with that of the reference one, that is, the specificity of the method for determining the sublingual tablets is satisfactory.

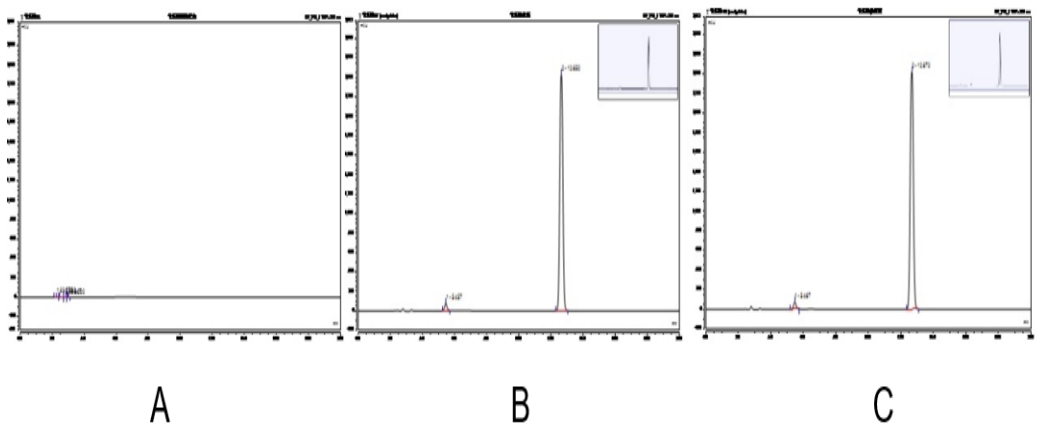

Figure 2. Chromatogram of each sample

3.2 Examination of linear relationships

As suggested in the figure 3, linear regression of scopolamine hydrobromide and armodafinil area (A) on the corresponding concentrations (C, μg/mL), respectively, indicate that both have good linear relationships.

The linear range of scopolamine hydrobromide is 1~50 μg/mL with the standard curve equation of A=0.2187C+0.0708, R^2=0.9993. While the linear range of armodafinil is 10~500 μg/mL with the standard curve equation of A=0.6702C-1.6855, R^2=0.9993.

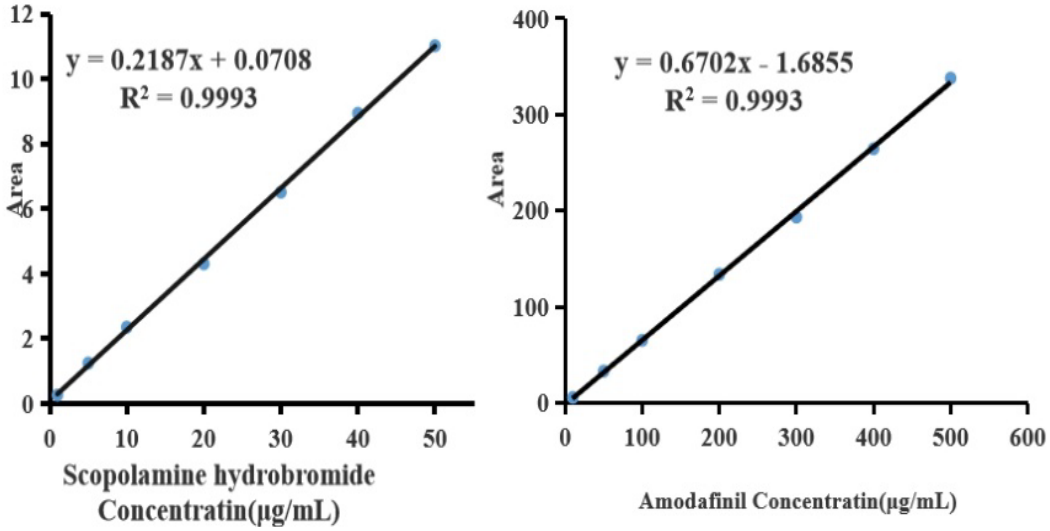

Figure 3. Standard curve

3.3 Precision of injection

Table 1 reveals that after preparing the solution containing 20 ug/mL of scopolamine hydrobromide and 200 ug/mL of armodafinil reference solution, and conducting the injection for 6 times, their RSD was all less than 2%; That is, the results meet the injection requirement of this method, and the sampling precision of this method is good.

Table 1. Results of injection precision for determining scopolamine hydrobromide and armodafinil content (n=6)

SUBJECT TO BE MEASURED	PEAK AREA						AVERAGE VALUE	RSD (%)
	1	2	3	4	5	6		
SH	4.84	4.82	4.75	4.91	4.95	4.96	4.87±0.08	1.64
AMDF	137.2	138.42	137.55	136.15	138.02	137.42	137.46±0.78	0.57

3.4 Intraday precision and inter-day precision

Table 2 reveals that scopolamine hydrobromide showcased fine precision at low concentration (5.00 μg/mL), medium concentration (20.00 μg/mL) and high concentration (40.00 μg/mL), concurrently, armodafinil manifests good precision at low concentration (50.00 μg/mL), medium concentration (200.00 μg/mL) and high concentration (400.00 μg/mL).

Both the intra-day precision and inter-day precision RSDs are minor than 2%, indicating that the method has good precision results and can be employed for the determination of scopolamine hydrobromide and armodafinil in sublingual tablets.

Table 2. Results of intra-day precision (n=5) and inter-day precision (n=3) for the determination of scopolamine hydrobromide and armodafinil content

C（μg/mL) of SH	Intraday Precision (%)	Inter-day Precision (%)	C（μg/mL) of AMDF	Intraday Precision (%)	Intra-day Precision (%)
5.00	1.68	0.26	50.00	0.81	1.48
20.00	1.65	1.68	200.00	0.59	1.65
40.00	0.63	1.37	400.00	0.18	1.75

3.5 Recovery of injected samples

As revealed in Tables 3 and 4, the recoveries are good at low concentration (50.00 μg/mL for armodafinil and 5.00 μg/mL for scopolamine hydrobromide), medium concentration (200.00 μg/mL for armodafinil and 20.00 μg/mL for scopolamine hydrobromide) and high concentration (400.00 μg/mL for armodafinil and 40.00 μg/mL for scopolamine hydrobromide).

The average recoveries are 98% and 102% with RSD less than 2%, indicating that the method has good recoveries effect and can be used to determining the content of compound sublingual tablets.

Table 3. Recovery results of the injected samples for the determination of scopolamine hydrobromide content (n=3)

C（μg/mL)	Recovery rate（%）			Average value	RSD（%）
	1	2	3		
5.00	99.62	99.40	101.21	100.08	0.99
20.00	100.31	101.15	98.13	99.86	1.56
40.00	100.40	99.82	100.10	100.11	0.29

Table 4. Results of injected samples for the determination of armodafinil content (n=3)

C（μg/mL)	Recovery rate（%）			Average value	RSD（%）
	1	2	3		
50.00	98.42	98.21	99.34	98.66	0.61
200.00	101.22	100.13	99.22	100.19	1.00
400.00	101.43	100.82	99.12	100.46	1.19

3.6 Placement stability of solution

The Table 5 demonstrates the RSD of compound scopolamine hydrobromide and armodafinil sublingual tablets is less than 2% at different time points, which revealed that the method is stable and is eligible to be used to simultaneously determining the scopolamine hydrobromide and armodafinil content.

Table 5. Stability results of the compound scopolamine hydrobromide armodafinil sublingual tablets solution

TIME	C（MG/ML）	
	SH	AMDF
0	2.95	498.20
8	3.05	499.15
12	2.95	501.72
24	3.01	498.05
SD	0.05	1.70
RSD（%）	1.64	0.34

3.7 Determination of the content of the test sample

The average contents of scopolamine hydrobromide and armodafinil are 298.16 mg/g and 123.52 mg/g respectively, which are 99.39% and 98.82% of

the indicated amounts. For more please see Table 6.

Table 6. The results of the determination of the compound scopolamine hydrobromide armodafinil sublingual tablets content

BATCH NO.	SH CONTENT (MG/TABLET)	AVERAGE CONTENT (MG/TABLET)	AMDF CONTENT (MG/TABLET)	AVERAGE CONTENT (MG/TABLET)
20211221	0.295		50.010	
20211222	0.315	0.295	49.920	50.010
20211223	0.305		50.125	

4. DISCUSSION

The present work concerns with the development and validation of stability indicating RP-HPLC method for simultaneous determination of modafinil and scopolamine hydrobromide in compound sublingual tablet without sample pretreatment and without interference from excipients. The developed method has advantage over any reported method in being able to determine the studied drug along with content with high sensitivity, selectivity and short analysis time using isocratic mobile phase for all components.

In addition, our follow-up study also proved that the parameters such as the mobile phase ratio in this analysis method are also suitable for the LC-MS/MS analysis of the plasma concentrations of scopolamine hydrobromide and armodafinil in the compound sublingual tablet we developed in animals. No interference from excipients was found in the establishment of the method. Therefore, we can draw a conclusion that the developed method can be easily applied to the quality analysis of the studied drugs.

The compound sublingual tablets in this experiment have been independently developed by this research group, which have also been subject to screening and optimization. Due to the fact that the raw materials are not available on the market, the armodafinil used in the experiment were synthesized by the research group and has been structurally validated.

In the prescription, the dosage of scopolamine hydrobromide is 0.3 mg/tablet and that of armodafinil is 50 mg/tablet. It is self-evident that the dosage difference between the two is quite large. Concentration range when taking into account dissolution testing, mine hydrobromide is set to 1~50 μg/mL, the linear range of armodafinil is set to 10~500 μ G/mμg/mLl when setting the concentration range of the standard curve.

That is to say, the ratio of scopolamine hydrobromide and armodafinil in the mixed solution is 1:10. It can be seen from the high performance liquid chromatogram that the peak area of scopolamine hydrobromide is much

smaller than that of armodafinil in the same solution. Scopolamine was used to determine the detection limit and the minimum quantification limit.

This experiment also examines the effect of different mobile phase systems and flow rates and columns on the results. When the mobile phase is methanol: buffer (25:75, pH 6) and the flow rate is 0.5 mL/min, the peak shape is cluttered; when the mobile phase is acetonitrile: buffer (25:75, pH 6), the flow rate is 0.5 mL /min, the peak shape has improved, and the two drugs can be detected at the same time, but there is a slight tailing and the retention time is too long; if the flow rate is adjusted to 1.0 mL/min, the peak shape of the chromatographic peak is good, and the resolution of each peak is good.

The peak time is moderate, and all the indicators basically meet the requirements. In order to obtain a better separation effect, different chromatographic columns were also investigated in this experiment. HIQci 8, Kromasil C18, Phenomenex C18, and Agilent C18 chromatographic columns were used to analyze the same test sample. The results show that the separation effect of each chromatographic column is basically the same, but Agilent C18 has higher column efficiency. Therefore, Agilent C18 was selected in this experiment. as an analytical column.

5. CONCLUSION

In the pursuit of developing a collaborative RP-HPLC method for the quantification of Modafinil and Scopolamine Hydrobromide in sublingual tablets, we have embarked on a journey that not only advances analytical science but also embodies the spirit of cooperation among key industry players. This endeavor has yielded valuable insights and outcomes that deserve recognition and reflection. Through meticulous research and experimentation, we have successfully developed a robust RP-HPLC method capable of accurately quantifying Modafinil and Scopolamine Hydrobromide in sublingual tablets.

The method's precision and reliability meet the highest industry standards, ensuring the quality and consistency of pharmaceutical products. The involvement of pharmaceutical companies, analytical instrument manufacturers, and regulatory authorities in this project has been pivotal. Their collective expertise, resources, and commitment to enhancing analytical methodology have demonstrated the immense potential of collaborative efforts in advancing pharmaceutical science. Such partnerships hold the key to overcoming complex challenges in the industry.

The ultimate beneficiaries of our research are the patients who rely on sublingual tablets for their medication. Our rigorous method development ensures that these patients receive consistent, safe, and effective treatments, promoting better health outcomes and enhanced patient compliance. In a highly regulated industry, our collaborative approach to method development aligns

with the principles of regulatory authorities, fostering transparency and adherence to stringent quality standards. This can streamline the approval process for pharmaceutical products and enhance their market accessibility. As we conclude this phase of collaborative research, it is imperative to recognize that the journey does not end here.

Continued collaboration, innovation, and adaptation to emerging analytical technologies will be essential to address evolving pharmaceutical challenges and maintain the highest standards of drug quality assessment. This project serves as a testament to the power of partnerships and shared expertise in driving progress within the industry. It underscores the importance of analytical precision in pharmaceuticals, with a steadfast commitment. to ensuring the well-being of patients.

As we move forward, let this collaborative endeavor inspire further innovations, partnerships, and advancements in pharmaceutical analysis for the betterment of healthcare worldwide.

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