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Determination of Equilibrium Solubility and Octanol-Water Partition Coefficient of α-asaronol

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Abstract

Objective: The objective of this study was to ascertain the equilibrium solubility and oil-water partition coefficient (lgP) of α-fine-octanol in disparate media, thereby establishing a theoretical foundation for the examination of α-fine-octanol formulations and pharmaceuticals. Methods: The equilibrium solubility and oil-water partition coefficient of *α*-asaronol were measured using UV spectrophotometry and high-performance liquid chromatography (HPLC). The lg*P* of *α*-asaronol was determined using the shake flask method. Results: The equilibrium solubility of α-fine-octanol at 37°C in four aqueous media, namely, distilled water, saline, phosphate buffer solution (pH 6.8 PBS), and pH 7.4 PBS, was 6090.3, 5361.8, 6300.7, and 5260.3 μg/mL, respectively. The equilibrium solubility of α-fine-octanol in the oil-phase medium, soybean oil, was found to be 8225.4 *μ*g/mL, which is greater than the equilibrium solubility of α-fine-octanol in the oil-phase medium, soybean oil, and the equilibrium solubility of α-fine-octanol in the oil-phase medium, soybean oil. Additionally, the octanol-water partition coefficient (lg*P*) of *α*-asaronol in these four aqueous media at 37°C ranged from 1 to 2. Conclusion: *α*-asaronol exhibits slight solubility in distilled water, physiological saline, pH 6.8 PBS, pH 7.4 PBS and soybean oil. It is a fat-soluble API with adequate water solubility and is classified as a highly transmissible drug. This characteristic renders it suitable for the development and utilization in the formulation of dosage forms intended for oral and rectal administration.

Keywords

α-asaronol; High Performance Liquid Chromatography Method; uv Spectrophotometry; Equilibrium Solubility; Octanol-water Partition Coefficient.

1. Introduction

α-Asaronol, chemically known as (E)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-ol, has the molecular formula C12H16O4. Its chemical structure is depicted in Figure 1. This compound appears as a white or off-white crystalline powder, devoid of any odor or special irritancy, with a melting point ranging from 66 to 68°C. It is readily soluble in solvents such as ethanol, dichloromethane, and acetone, but only slightly soluble in low-polarity solvents like water and petroleum ether[1].

Since the discovery of *α*-asaronol as a metabolite of orally administered *α*-asaronol in rats by Zheng Xiaohui in 2014[2]and Cartus in 2015[3], research on *α*-asaronol has been the focus of considerable attention. Subsequent studies by relevant researchers have gradually revealed that α-asaronol exhibits superior anti-epileptic activity[4-5], LDH inhibitory activity[6-7], and neurotoxicity[8] compared to similar anti-epileptic drugs abroad, such as stiripentol. Although stiripentol has been found to have some adjunctive therapeutic effects in Dravet syndrome, there is a lack of systematic evidence to support its efficacy and safety. After the continuous

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optimization and improvement of the synthesis route by Dickson[9], Zheng Xiaohui[10], and Zhang Qunzheng[11], the previously encountered issues of inconvenient operation and low yield in the synthesis of α-asaronol have been overcome. A synthesis process with high yield and simple post-treatment has been developed.

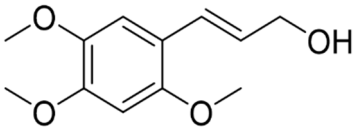

Fig 1. The structural of *α*-asaronol

The equilibrium solubility and oil-water partition coefficient of a drug are critical parameters in the design of drug formulations[12]. Drugs require not only an appropriate degree of lipophilicity to permeate biological membranes, but also a certain level of water solubility to facilitate its transport within bodily fluids, to reach the target site and bind to receptors to exert its pharmacological effects. Therefore, the equilibrium solubility and oil-water partition coefficient of a drug play a pivotal role in selecting the appropriate dosage form and determining the mixing ratio of oil and water phases. In this study, the equilibrium solubility and apparent partition coefficient of *α*-asaronol in various media were determined using ultraviolet spectrophotometry and high-performance liquid chromatography[13]. These measurements provide a foundation for the subsequent biopharmaceutical classification of *α*-asaronol.

2. Instruments and Reagents

2.1. Instruments

THZ-98A Constant Temperature Oscillator (Wandasheng Laboratory Instruments Co., Ltd.), TG16-WS Benchtop High-Speed Centrifuge (Keli Yixiang Instrument Equipment Co., Ltd.), Leici PHB-4 Portable pH Meter (Wuxi Leici Instrument Co., Ltd.), 881 UV-Vis Spectrophotometer (Metrohm, Switzerland), Agilent 1100 High-Performance Liquid Chromatograph,Molelement Element Ultrapure Water System (Shanghai Molelement Biotechnology Co., Ltd.).

2.2. Reagents

α-Asaronol (self-made), methanol (chromatographic grade, Thermo Fisher Scientific Inc.), potassium dihydrogen phosphate (analytical reagent grade, Tianjin Damao Chemical Reagent Factory), dichloromethane (analytical reagent grade, Longxi Science Co., Ltd.), n-octanol (analytical reagent grade, Tianjin Comin Chemical Reagent Co., Ltd.), borax (analytical reagent grade, Xilong Science Co., Ltd.), normal saline (injection grade, Shandong Qidu Pharmaceutical Co., Ltd.).

3. Methods and Results

3.1. Preparation of Different Buffers

3.1.1. Preparation of Normal Saline (0.9% NaCl Solution)

0.9 g NaCl was weighed precisely, and the volume was fixed in a 100 mL measuring flask with water; distilled water was prepared by the laboratory ultrapure water mechanism.

3.1.2. Preparation of the Reference Substance Solution of α-asaronol

A quantity of 50 milligrams of α-fine octanol was weighed and subsequently diluted with methanol in a 100-milliliter measuring flask to yield a control solution containing approximately 500 micrograms per milliliter of α-fine octanol.

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3.1.3. Preparation of Simulated Rectal Fluid (pH 6.8 PBS)

0.68 g of KH2PO4 precisely weighed has been dissolved in 90 mL of water. the pH must be adjusted to 6.8 ± 0.1 with a 0.2 mol/L NaOH solution. Finally, the solution must be condensed into a 100 mL measuring flask.

3.1.4. Preparation of Simulated Rectal Fluid (pH 7.4 PBS)

The precise weight of 0.68 g of KH2PO4, dissolved in 90 mL of water and adjusted to a pH of 7.4 ± 0.1 with a 0.2 mol/L NaOH solution, was fixed in a 100 mL measuring flask.

3.1.5. Preparation of the Equilibrium Saturated Solution of α-asaronol

A 10-mL quantity of distilled water, saline (pH 6.8), and pH 7.4 phosphate-buffered saline (PBS) should be measured and transferred to a 10-mL EP tube. Subsequently, 100 mg of α-octanol should be weighed in and added to each sample. It is imperative that each sample be prepared thrice in parallel, vortexed for 10 m, and then placed in a 37 ± 1.0°C shaking box for 72 h to equilibrate, thereby obtaining the equilibrium saturated solution.

3.2. Establishment and Validation of the Analytical Method

3.2.1. Chromatographic Conditions

Agilent C18 chromatographic column (4.6 mm × 250 mm, 5 μm); Use methanol (A) and water (B) for gradient elution: from 0 min (40% A-60% B) to 20 min (0% A-100% B), and maintain at (0% A-100% B) from 20 min to 25 min; The flow rate is 0.8 mL·min^{-1}; The column temperature is set at 35 °C; The detection wavelength is 315 nm; The injection volume is 10 μL.

3.2.2. Specificity

Blank solvent (methanol) and the reference substance solution of α-asaronol were injected under the chromatographic conditions described in 2.2.1, and the chromatograms were recorded. The chromatogram of the blank methanol is shown in Figure 2. It indicates that the blank methanol does not interfere with the determination of α-asaronol. The chromatogram of α-asaronol is shown in Figure 3. The retention time of α-asaronol is 5.3 min. The chromatographic peak shape is good, and the resolution of the main peak meets the requirements.

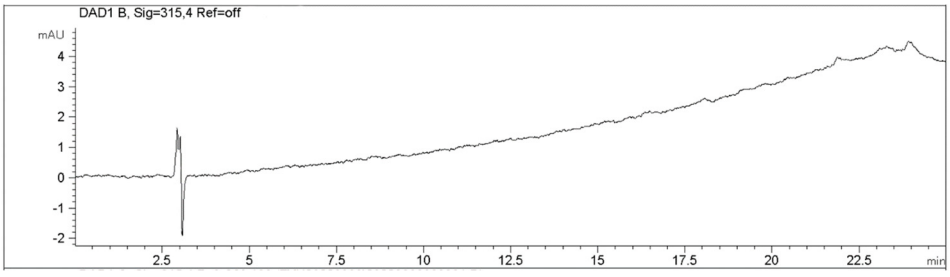

Fig 2. Liquid chromatogram of blank methanol

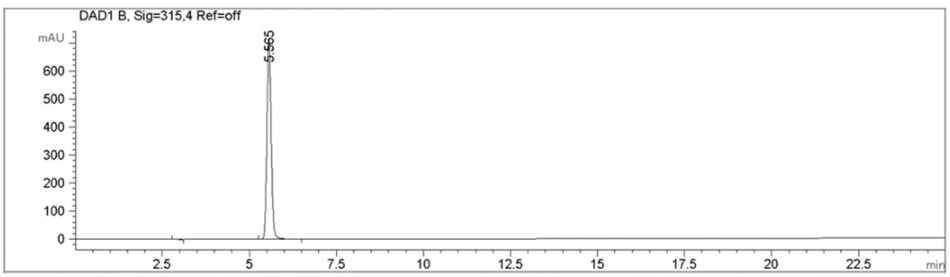

Fig 3. Liquid chromatogram of α-asaronol

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3.2.3. Investigation of the linear relationship

Appropriate amounts of the reference substance stock solution of *α*-asaronol should be precisely measured. A series of reference substance solutions with concentrations of 10, 25, 50, 75, 100, and 250 μg·mL^{-1} were prepared by the dilution method, and vortex for 5 m. Methanol was used as a blank control, and 10 μL of the sample was injected from the low concentration to the high concentration according to the chromatographic conditions under 2.2.1, and the peak area was recorded. Linear regression was conducted with the mass concentration X (μg·mL^{-1}) as the abscissa and the peak area value (Y) as the ordinate. The standard curve equation of *α*-asaronol is obtained as Y = 20.744X + 35.436, with r^2 = 0.9993. The results show that within the concentration range of 10-250 μg·mL^{-1}, there is a good linear relationship between the concentration of *α*-asaronol and the peak area.

3.2.4. Precision Test

3.2.4.1 Repeatability

Accurately weigh 10.0 mg of *α*-asaronol sample and dissolve it in anhydrous methanol, then dilute to volume in a 100 mL volumetric flask to prepare a test solution with a concentration of 100 *μ*g/mL (equivalent to 100% concentration level). Six parallel samples were prepared and injected into the liquid chromatograph under the chromatographic conditions specified in Section 2.2.1 for analysis. The peak areas were recorded, and the relative standard deviation (RSD) of the *α*-asaronol peak area was 0.05%. This demonstrates excellent repeatability of the method and effectively avoids random errors.

3.2.4.2 Intermediate Precision

Six analysts tested *α*-asaronol at 0.5-hour intervals. Six parallel samples of the test solution (100 *μ*g/mL, equivalent to 100% concentration level) were prepared and injected into the liquid chromatograph under the chromatographic conditions described in Section 2.2.1. The average content of *α*-asaronol determined by the six analysts across different time intervals was 99.92%, with a relative standard deviation (RSD) of 0.04%. These results indicate high intermediate precision of the method, ensuring the accuracy and reliability of the results.

3.2.5. Recovery test

Precisely weigh the *α*-asaronol raw material and prepare test solutions at three different concentrations (80 *μ*g·mL^{-1}, 100 *μ*g·mL^{-1}, and 120 *μ*g·mL^{-1}) with a methanol solution. Each concentration was measured three times under the chromatographic conditions described in 2.2.1. The difference between the average of the measurement results and the true value of the *α*-asaronol samples at the three different concentrations determined by this liquid chromatography detection method was 0.1%, and the relative standard deviation (RSD) was 0.05%. These results indicate that the method has good accuracy.

3.2.6. Stability Test

Accurately weigh 75.0 mg of *α*-asaronol sample and dissolve it in anhydrous methanol, then dilute to volume in a 100 mL volumetric flask to prepare a test solution with a concentration of 750 *μ*g/mL. Inject the solution into the liquid chromatograph under the chromatographic conditions specified in Section 2.2.1 after storage at room temperature for 0, 2, 4, 6, 8, 12, and 24 h, respectively. The average content of *α*-asaronol determined by this method was 99.99%, with a relative standard deviation (RSD) of 0.09%. These results demonstrate excellent stability of the test solution within 24 h.

3.2.7. Limit of Detection (LOD) and Limit of Quantification (LOQ)

Take 1 mL of a 1 mg/mL *α*-asaronol solution and perform stepwise dilution. Inject the diluted solutions into the liquid chromatograph under the chromatographic conditions specified in Section 2.2.1 for analysis, the corresponding concentration when the signal-to-noise ratio (S/N) is 3 (in analytical chemistry) is defined as the limit of detection. The limit of detection of *α*-

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asaronol is determined to be 0.05 $\mu g \cdot mL^{-1}$. The corresponding concentration when S/N = 10 is defined as the limit of quantification, and the limit of quantification of α-asaronol is found to be 0.1 $\mu g \cdot mL^{-1}$.The results indicate that the chromatographic conditions used have good detection sensitivity for α-asaronol related substances at the test sample concentration.

3.3. Determination of the Equilibrium Solubility of α-asaronol

3.3.1. Determination of the Equilibrium Solubility of α-asaronol in Aqueous Medium

Excess *α-asaronol* API was placed in a 10 mL stoppered glass test tube. Two milliliters of four aqueous media—distilled water, normal saline, pH 6.8 PBS, and pH 7.4 PBS—were added separately. The tubes were shaken in a 37°C incubator for 72 h, followed by centrifugation. The supernatant was collected, filtered, diluted, and injected into the liquid chromatograph under the chromatographic conditions specified in Section 2.2.1. Chromatograms were recorded, and the equilibrium solubility was calculated based on the measured concentrations. Since α-asaronol is nearly insoluble in water, this study aimed to evaluate its dissolution behavior in different aqueous media. The results are summarized in Table 1.

Table 1. Equilibrium solubility of α-asaronol in different media($x \pm SD, n=3$)

Solvent	Equilibrium solubility($\mu g \cdot mL^{-1}$)
Distilled water	6090.3±173.2
Normal saline	5361.8±119.2
pH 6.8 PBS	6300.7±295.8
pH 7.4 PBS	5260.3±5.9

3.3.2. Investigation of the Equilibrium Solubility of α-asaronol in Soybean Oil

3.3.2.1 Linearity Experiment

Table 2. Linear relationship of α-asaronol in dichloromethane and methanol

Concentration($\mu g \cdot mL^{-1}$)	Absorbance 1	Absorbance 2
5	0.169	0.174
10	0.382	0.373
15	0.537	0.532
20	0.715	0.708
25	0.868	0.855
40	1.442	1.434
50	1.784	1.760
75	2.387	2.390
100	2.614	2.602
250	2.674	2.667

Accurately weigh 125 mg of α-asaronol and dissolve it in dichloromethane (DCM) and methanol separately, then dilute to volume in 500 mL volumetric flasks to prepare stock solutions of 250

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μg/mL. Precisely pipette 1, 2, 3, 4, 5, 8, 10, 15, 20, and 50 mL aliquots of the stock solutions into 50 mL volumetric flasks, and dilute to obtain serial test solutions with concentrations of 5, 10, 15, 20, 25, 40, 50, 75, 100, and 250 μg/mL. Using DCM and methanol as blank controls, the test solutions were analyzed by UV spectrophotometry at a detection wavelength of 315 nm. A linear regression analysis was performed with absorbance (Y) as the ordinate and the injection concentration (X, μg/mL) of α-asaronol as the abscissa. The standard curves for α-asaronol were established, and the results are summarized in Table 2 (entries 1 and 2 correspond to DCM and methanol as solvents, respectively).

The results show that when the concentration of α-asaronol exceeds 20 $\mu g \cdot mL^{-1}$, the linear relationship between the concentration and absorbance weakens, and the absorbance value exceeds the optimal response range (0.8) of the spectrophotometer. Therefore, linear regression analysis was performed on the data of α-asaronol with a detection concentration less than 20 $\mu g \cdot mL^{-1}$. The results are shown in Figure 4.

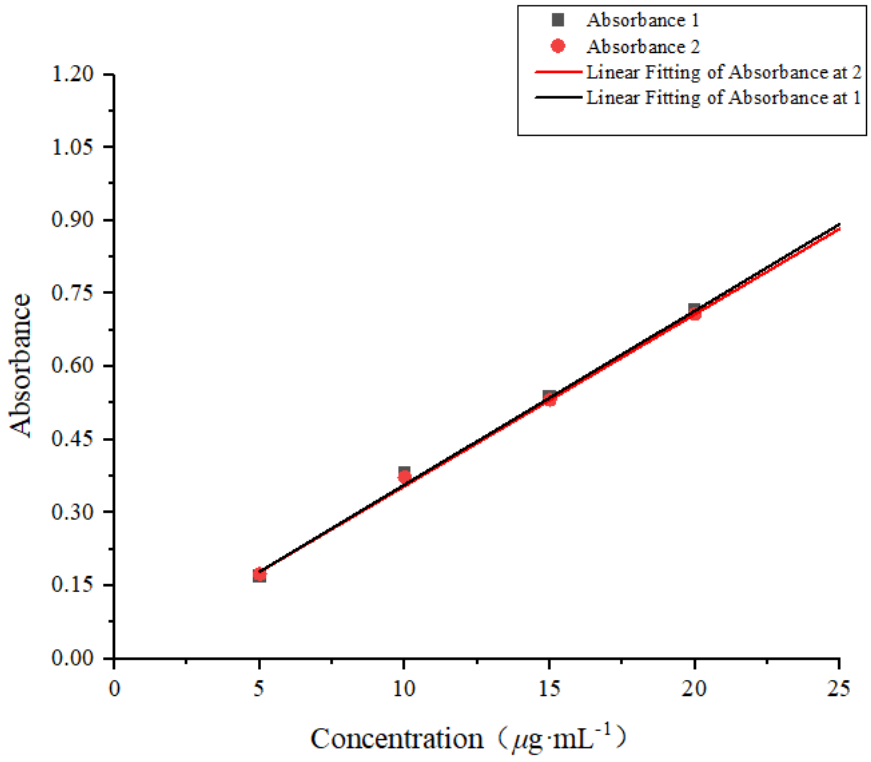

Fig 4. Standard curve with self-control

It can be obtained that when dichloromethane is used as the solvent, the standard curve of α-asaronol is Y1 = 0.0357X + 0.001, with r^2 = 0.9992. When methanol is used as the solvent, the standard curve of α-asaronol is Y2 = 0.0353X + 0.002, with r^2 = 0.9991. The results show that within the concentration range of 5-20 $\mu g \cdot mL^{-1}$, there is a good linear relationship between the concentration of α-asaronol and the absorbance.

3.3.2.2 Determination of the Equilibrium Solubility of α-asaronol in Soybean Oil

Excess α-asaronol (approximately 200 mg) was placed in a 25 mL centrifuge tube. Precisely 10 mL of soybean oil was added, and the mixture was vortexed for 10 m. Subsequently, it was shaken in a shaking incubator at 37 ± 1.0°C for 72 h to allow equilibration. The equilibrated saturated solution was then obtained. After sampling, perform centrifugation, take the supernatant and filter it. Then take 0.5 mL of the subsequent filtrate and dilute it step-by-step with DCM. Detect its absorbance using an ultraviolet spectrophotometer until the absorbance value (A) drops below 1.0. Dilute the saturated concentration to one-ten-thousandth as the test sample solution. At this time, there is a good linear relationship between the concentration of

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α-asaronol and its absorbance. Use soybean oil diluted to one-ten-thousandth with DCM as the blank control, and detect it with an ultraviolet spectrophotometer. Perform parallel measurements 3 times at a detection wavelength of 315 nm. The results are shown in Table 3.

Table 3. Equilibrium solubility of *α*-asaronol in soybean oil($x \pm SD, n=3$)

Sample	Absorbance	Concentration($\mu g \cdot mL^{-1}$)	$x \pm SD$ ($\mu g \cdot mL^{-1}$)
1	0.273	7619.32	8225.38 ± 438.48
2	0.301	8414.77	
3	0.309	8642.05	

3.4. Investigation of the Oil-Water Partition Coefficient of α-asaronol

3.4.1. Pre-saturation Treatment

Both n-octanol and aqueous media must be pre-saturated. Four 250 mL storage bottles were prepared, each containing 100 mL of n-octanol and 100 mL of an aqueous medium (distilled water, normal saline, pH 6.8 PBS, or pH 7.4 PBS). The bottles were placed in a shaking incubator at 37 ± 1.0°C and shaken for 48 h to achieve equilibrium. After standing to allow phase separation, the following were obtained.

3.4.2. Determination of the Oil-Water Partition Coefficient of Low-Concentration α-asaronol

Precisely weigh 10 mg of the *α*-asaronol bulk drug and dissolve it in 100 mL of the aqueous phase-saturated n-octanol to obtain a test sample stock solution with a concentration of 100 $\mu g \bullet mL^{-1}$. Prepare three parallel samples. Precisely measure 10 mL of the test sample stock solution and 10 mL of each n-octanol-saturated aqueous phase medium into a 25mL EP tube. Sonicate for 10 m, and then place it in a shaking incubator at 37 ± 1.0 °C to oscillate and reach equilibrium for 48 h. After standing for layer separation, take the upper oil phase, centrifuge it, take the supernatant and filter it. Dilute it with methanol to obtain the test sample solution. Use the aqueous phase-saturated n-octanol as the blank control, and measure it with an ultraviolet spectrophotometer. Conduct parallel measurements three times at a detection wavelength of 315 nm.

Calculate their concentrations respectively, and then calculate the apparent oil-water partition coefficient The calculation formula is as follows:

$$P_{apps}=C_O/C_w$$

C_O represents the concentration of α-asaronol in n-octanol at equilibrium, and C_w represents the concentration of α-asaronol in the aqueous phase at equilibrium. The results are shown in Table 4.

Table 4. Oil-water partition coefficient of low concentration *α*-asaronol in different media ($x \pm SD$, $n=3$)

Medium	lg*P*
Distilled water	1.389 ± 0.014
Normal saline	1.759 ± 0.088
pH 6.8 PBS	1.377 ± 0.024
pH 7.4 PBS	1.574 ± 0.069

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3.4.3. Determination of the Oil-Water Partition Coefficient of α-asaronol at Saturated Concentration

Take 12 mL of n-octanol saturated with different aqueous phases, add an excess amount (3 g) of *α*-asaronol. After sonicating for 20 m, place it in a shaking incubator at 37 ± 1.0 °C and shake for 48 h to reach equilibrium, obtaining an n-octanol solution of *α*-asaronol at saturated concentration. Centrifuge the n-octanol solution of *α*-asaronol at saturated concentration, transfer and filter the supernatant. Take 0.5 mL of the subsequent filtrate and dilute it step-by-step with methanol. Measure its absorbance with an ultraviolet spectrophotometer to obtain the concentration when the absorbance drops below 1.0 (i.e., one-ten-thousandth of the corresponding saturated concentration). There is a good linear relationship between the concentration of *α*-asaronol and its absorbance. Conduct parallel measurements three times to obtain the saturated solubility of *α*-asaronol in n-octanol under different media. Precisely measure 10 mL of the subsequent filtrate and 10 mL of each n-octanol-saturated aqueous phase medium into a 25-mL EP tube. Sonicate for 10 m, then place it in a shaking incubator at 37 ± 1.0 °C and oscillate for 48 h to reach equilibrium. Take out the equilibrium solution, let it stand for layer separation. Take the upper oil phase, centrifuge it, take the supernatant and filter it. Dilute it to one-ten-thousandth with methanol as the test sample solution. Use the n-octanol saturated with each aqueous phase as the blank control, and measure it with an ultraviolet spectrophotometer. Conduct parallel measurements three times to determine the concentration c (n-octanol) of *α*-asaronol in the oil phase at a detection wavelength of 315 nm. The results are shown in Figure 5.

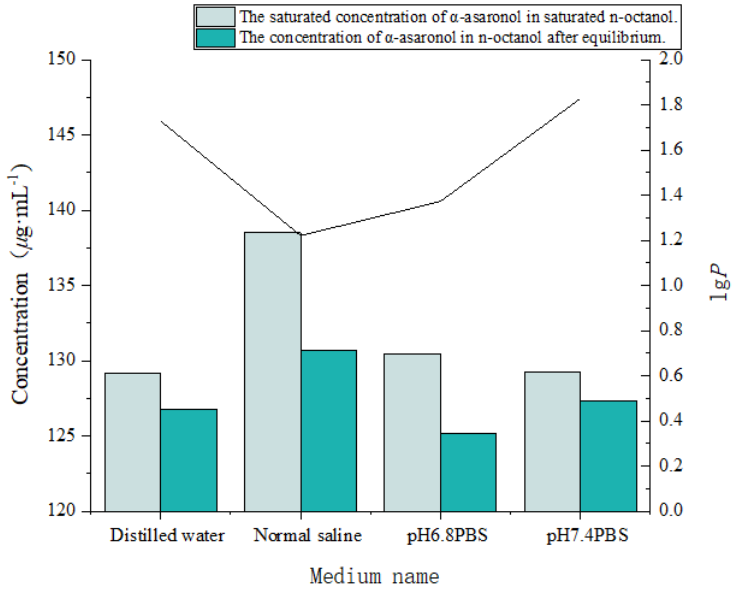

Fig 5. Concentration of *α*-asaronol drug in different media

4. Discussion

4.1. Establishment of the Method

This study established an HPLC method for the content determination of *α*-asaronol. Additionally, UV spectrophotometry and HPLC were employed to measure the equilibrium solubility and oil-water partition coefficient of *α*-asaronol in different media. The developed methodology provides foundational data to support further research on the physicochemical and pharmaceutical properties of *α*-asaronol, as well as formulation development, process optimization, and quality control studies for *α*-asaronol-based preparations.

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4.2. Equilibrium Solubility

Equilibrium solubility refers to the maximum concentration of a solute dissolved in a solvent when a dynamic equilibrium is reached between the undissolved solute and the dissolved phase. Both solubility and equilibrium solubility play critical roles in drug disposition. The primary pathway for drug absorption is passive transport across cell membranes, and the rate of passive transport depends on the drug's permeability and solubility[14]. α-asaronol is sparingly soluble in the four aqueous media tested: distilled water, normal saline, pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer. However, it exhibits improved solubility in pH 6.8 simulated rectal fluid.

Soybean oil, rich in fatty acids and phospholipids, demonstrates strong drug-loading capacity, solubility enhancement, and controlled release properties. Its excellent biocompatibility, compatibility with vitamins and other pharmaceuticals, low irritation potential, and absence of significant toxic or side effects in humans make it an ideal candidate as the oil phase in dispersed microsystems for α-asaronol formulation development. Specifically, it serves as a drug carrier in emulsion systems to dissolve and stabilize α-asaronol[15,16].

4.3. Oil-Water Partition Coefficient

The oil-water partition coefficient is recognized as a critical parameter for evaluating drug membrane permeability and lipid solubility [17]. The determination of log*P* in vitro is conducted to simulate the distribution of drugs between aqueous and biomembrane phases in vivo. n-Octanol, whose solubility parameters are matched to those of cellular biomembranes, is utilized as the solvent to mimic the biological membrane phase, enabling the prediction of intestinal absorption[18,19]. Drugs with logP values between -1 and 2 are widely considered to exhibit balanced solubility and membrane permeability, which facilitates cellular absorption and transport[20,21]. Similarly, drugs with logP values between 0 and 3 are more likely to be absorbed in the intestinal tract.For α-asaronol, logP values in simulated rectal fluid (pH 6.8–7.4) are observed to range from 0 to 3, indicating favorable lipophilicity and efficient membrane absorption. Notably, log P values between 1 and 2 in aqueous media are demonstrated by α-asaronol, highlighting its dual hydrophilic-lipophilic properties. This qualifies it as an ideal lipid-soluble API with good aqueous solubility[12], meeting the requirements for rectal drug delivery.

From the equilibrium solubility and log P results, the following conclusions are drawn: The highest log P is achieved by *α*-asaronol at pH 7.4 within the tested range (pH 6.8–7.4), suggesting greater stability and fewer impurities in mildly alkaline environments. pH 7.4 conditions are recommended for formulation development. Advanced pharmaceutical technologies, such as microemulsions, micelles, liposomes, and nanostructured lipid carriers, are proposed to be integrated to enhance solubility, gastrointestinal absorption, and clinical efficacy.

Acknowledgments

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References

[1] Feng Mingnan. Research on the Quality Standard and Stability of Anti-Epileptic Candidate Drug 93S (0/1) [D]. Xi'an: Xi'an University of Petroleum, 2022.

[2] Zheng Xiaohui, Bai Yajun, Qin Fanggang, et al., α-asaronol and its preparation method and application. 10692696.9 [P]. 2014-11-26.

[3] Cartus A T, Dieter S. Metabolism of the carcinogen alpha-asarone in liver microsomes[J]. Food and Chemical Toxicology, 2015, 87(9): 103~112.

[4] Zhao Shizheng. Animal experiments on the anti-micro-pain effect of α-asaronol and exploration of its mechanism [J]. Journal of Integrated Traditional and Western Medicine, 1984, 4(8): 490-490.

[5] Hu Jinguan, Gu Jian, Wang Zhiwang. Experimental study on the effects of Acorus tatarinowii and its active components on the central nervous system [J]. Pharmacology and Clinical of Chinese Materia Medica, 1999, 15(3): 19-21.

[6] Zhou Daxing, Bao Zuxiao, Wu Xiongsheng. Anticonvulsant effect of the ethanol extract of Acorus tatarinowii [J]. Chinese Journal of Modern Applied Pharmacy, 1999, 16(5): 641-642.

[7] Zeng Min. Metabolism of the anti-epileptic active substance α-asaronol in normal and epileptic model rats [D]. Xi'an: Northwest University, 2017.

[8] Qin Fanggang. Design, synthesis, and anti-epileptic activity study of α-asaronol and its derivatives [D]. Xi'an: Northwest University, 2015.

[9] Benjamin D, Dickson. Synthesis of 2,3-syn-diarylpent-4-enamides via acyl-Claisen rearrangements of substituted cinnamyl morpholines: application to the synthesis of magnosalicin[J]. Tetrahedron Letters, 2012, 53(33):4464~4468.

[10] Zheng Xiaohui, Bai Yajun, Qin Fanggang, et al. α-asaronol and its preparation method and application [P]. CN: 104529724 A, 2015.04.22.

[11] Zhang Qunzheng, Wang Shichang, Ke Congyu, et al. Synthesis method of α-asaronol acetate and α-asaronol [P]. CN: 113387804 A, 2021.09.14.

[12] Han Yan, Chen Boying, Su Na, et al. Determination of the equilibrium solubility and apparent oil-water partition coefficient of Ambroxol Hydrochloride [J]. Journal of Drug Evaluation, 2016, 39(4): 615.

[13] Zhou Yuhao. Research on the formulation process and quality standard of α-asaronol preparations [D]. Xi'an: Xi'an University of Petroleum, 2023.

[14] FALLER B, ERTL P. Computational approaches to determine drug solubility[J]. Advanced Drug Delivery Reviews, 2007, 59(07): 533~545.

[15] New R R C, Kirby C J. Solubilisation of hydrophilic drugs in oily formulations[J]. Advanced Drug Delivery Reviews, 1997, 25: 59~69.

[16] Tamilvanan S. Oil-in-water lipid emulsions: implications for parenteral and ocular delivering systems[J]. Progress in Lipid Research, 2004, 43: 489~533.

[17] Wang Xue, Chen Hua, Yin Jie, et al. Determination of the equilibrium solubility and oil-water partition coefficient of Codeine Phosphate [J]. Journal of Pharmaceutical Analysis, 2019, 39(4): 749-754.

[18] Qian Guiying, Geng Liuqing, Shan Jinjun, et al. Determination of the physicochemical constants of total coumarins from Zishimai [J]. Journal of Information on Traditional Chinese Medicine, 2006, 13(10): 52-53.

[19] Zhang Minmin, Liu Chong, Chen Wen, et al. Determination of the equilibrium solubility, oil-water partition coefficient, and dissociation constant of Acacetin [J]. Shijizhen National Medicine and Pharmacy, 2020, 31(5): 1087.

[20] Zhu Rongyue, Chang Daoxiao, Sui Hong, et al. Determination of the equilibrium solubility and apparent oil-water partition coefficient of Lutein by HPLC [J]. Journal of Pharmaceutical Research, 2018, 37(7): 388.

[21] Zhang Huihui, Shi Yang, Zhang Xiaoxia, et al. Determination of the equilibrium solubility and oil-water partition coefficient of Punicalagin [J]. Journal of Xinjiang Medical University, 2018, 41(2): 225.