

ANALYSIS OF APPROACHES TO THE DEVELOPMENT AND VALIDATION OF THE METHODS OF ANALYSIS OF BISOPROLOL IN DRUGS AND BIOLOGICAL LIQUIDS

Introduction. Analytical method development is increasingly being introduced into fundamental pharmaceutical research, taking into account their high sensitivity, accuracy, specificity and expressiveness. Search criteria was analytical method development for bisoprolol. Literature survey was done in range of years 1990–2018 to make the review updated and comprehensive and to show the new approaches to the development of the methods of analysis of bisoprolol. The sources were world recognized journals and key words used as filter were bisoprolol, method development, validation, spectrophotometry, HPLC, UHPLC. The current review is created with an intention to focus on the advantage of HPLC. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC. In additional, analysis of approaches to the development of the methods of analysis of bisoprolol in drugs and biological liquids has been shown that HPLC is the most suitable method for analyses of bisoprolol in substances, drugs, biological liquids to perform routine analysis of medicines, pharmacokinetic (bioequivalence in vivo), dissolution test for final dosages forms (bioequivalence in vitro, bio-waiver procedure).

The aim of the study – to analyze approaches to the development and validation of the methods of analysis of bisoprolol in drugs and biological liquids.

Conclusions. In light of the benefits discussed in this review, we can conclude that analysts are constantly working on developing new methods of analysis of bisoprolol in drugs and biological liquids and on their optimization in order to save time and consumables, which also ensures the efficiency of the developed methodology. Literature survey revealed that a number of methods have been reported for estimation of bisoprolol individually or in combination with other drugs. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC.

KEY WORDS: bisoprolol; spectrophotometric method; High-Performance Liquid Chromatography; quantitative analysis; validation.

Bisoprolol is a synthetic, beta1-selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing activity or intrinsic sympathomimetic activity in its therapeutic dosage range. The chemical name of bisoprolol fumarate is 1-(propan-2-ylamino)-3-[4-(2-propan-2-yloxyethoxymethyl) phenoxy]propan-2-ol (Fig.). The most prominent effect of bisoprolol fumarate is the negative chronotropic effect, resulting in a reduction in resting and exercise heart rate. There is a fall in resting and exercise cardiac output with little observed change in stroke volume, and only a small increase in right atrial pressure, or pulmonary capillary wedge pressure at rest or during exercise.

The State Pharmacopoeia of Ukraine (SPHU) does not have a monograph on the substance of bisoprolol fumarate or on ready medical form. However, the United States Pharmacopoeia [1] regulates

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the definition of bisoprolol fumarate in substances and tablets. For identification, TLC is proposed (mobile phase – a mixture of dichloromethane, methanol and ammonia solution (70:10:0.8)). For the quantitative determination of bisoprolol fumarate in tablets – HPLC/UV. Chromatographic conditions for the determination of drug of Bisoprolol Fumarate, tablets are given in the monograph of the United States Pharmacopoeia, where chromatographic column of L7 category and mobile phase consisting of three components: heptafluorobutanoic acid,

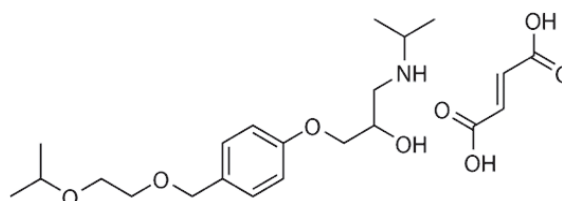


Fig. Chemical structure of bisoprolol fumarate.

diethylamine, formate acid are used. Solvent – a mixture of water and acetonitrile (65:35), mobile phase rate – 1 ml/min, detection of wavelength – 273 nm. The proposed method of the United States Pharmacopoeia requires long sample preparation.

The European Pharmacopoeia [2] has a monograph on the substance of bisoprolol fumarate. Identification of bisoprolol fumarate EPh regulates to perform the absorption spectrophotometry in the infrared region and the quantitative determination – acidimetry non-aqueous titration.

The scientific literature describes the methods of quantitative determination of bisoprolol fumarate in drugs and biological fluids by spectrophotometry [3–12] and chromatography methods [12–35].

Ukrainian scientists Yu. M. Zhuk, S. O. Vasiuk, I. M. Keitlin developed UV-spectrophotometric method for the determination of bisoprolol in tablets by reaction with timol blue. The reaction product had a maximum absorption at 420 nm. LOD amounted to 2.19 µg/ml, correlation coefficient – 0.9999 [3].

R. Sahu et al. described the spectrophotometric method for the determination of bisoprolol fumarate and hydrochlorothiazide in tablets. The maximum absorption of bisoprolol was observed at a wavelength of 223 nm, and the hydrochlorothiazide – 271.6 nm. The method was linear in the range of concentrations of bisoprolol 2–6 µg/ml and hydrochlorothiazide – 5–15 µg/ml, respectively. The correlation coefficient of bisoprolol was 0.9994, hydrochlorothiazide – 0.9971. The developed method has been successfully applied for routine determination of bisoprolol fumarate and hydrochlorothiazide in tablets [5].

A. S. Atul et al. also proposed spectrophotometric method for the determination of bisoprolol fumarate and hydrochlorothiazide in tablets. The maximum absorption of bisoprolol was observed at a wavelength of 224 nm, and hydrochlorothiazide – 273 nm. The method was linear in the range of bisoprolol concentrations of 3–21 µg/ml, and hydrochlorothiazide – 3–18 µg/ml, respectively. The method has been completely validated and used to determine bisoprolol fumarate and hydrochlorothiazide in drugs [6].

Scientists S. T. Ulu and E. Kel developed the spectrophotometric method for the determination of bisoprolol, which was based on interaction with 7,7,8,8-tetracyanohydromethane and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Solutions of the complex are colored in the corresponding colors and are subject to the Bouguer-Lambert-Beer's law in the concentration range of 10–60 µg/ml and 10–80 µg/ml, respectively. The proposed method has been successfully applied to determine bisoprolol in medical form [7].

A. D. Panainte et al. described the spectrophotometric method for the determination of bisoprolol by reaction with picric acid. The reaction product had a maximum absorption at 420 nm. The method was linear in the range of concentrations of 5–120 µg/ml, the correlation coefficient was 0.9992 [8].

Scientists S. T. Kumbhar, P. P. Shinde, D. B. Shinde, P. B. Solankar proposed the spectrophotometric method of determination of bisoprolol, which was based on the interaction of iron (III) with chloride and potassium with ferricyanide with the formation of blue chromogen with a maximum absorption of 770 nm. Solutions are subject to the Bouguer-Lambert-Beer's law in the concentration range of 1–13 µg/ml. The proposed method has been successfully applied to determine bisoprolol in tablets [9].

R. B. Kakde et al. developed the spectrophotometric method for the determination of bisoprolol and amlodipine in drugs. The maximum absorption of bisoprolol was observed at a wavelength of 222 nm, amlodipine – 365 nm. The method was linear in the range of concentrations of 5–100 µg/ml of both analytes. The developed method was validated and successfully applied for the routine determination of bisoprolol and amlodipine in drugs [10].

A. D. Panainte et al. described HPLC/UV method for the determination of bisoprolol in tablets using SB-C18Nucleosil column (125×4 mm) and mobile phase – a mixture of methanol, acetonitrile, 45 mM of potassium dihydrogen phosphate buffer solution pH 3.0 (30:25:45, v/v/v), the flow rate – 0.3 ml/min, the detection wavelength – 225 nm. Bisoprolol retention time was 2.32 min. The method was linear in the range of concentrations of 0.3–10 µg/ml. The developed method has been successfully applied to study the bioequivalence of drugs containing bisoprolol [14].

S. Shaikh et al. proposed HPLC/UV method for the determination of bisoprolol and hydrochlorothiazide in tablets using mobile phase – a mixture of 0.1 M phosphate buffer solution, acetonitrile, tetrahydrofuran (85:10:5, v/v/v), flow rate – 1.0 ml/min, wavelength detection – 225 nm. Total retention time was less than 10 minutes. The method was linear in the range of concentrations of bisoprolol 50–150 µg/ml and hydrochlorothiazide – 125–375 µg/ml, respectively. The developed method has been successfully applied for the determination of bisoprolol and hydrochlorothiazide in tablets [15].

Reverse-phase HPLC/UV method for the determination of bisoprolol and hydrochlorothiazide in drugs was developed by S. J. Joshi et al. In the method there are used the Inertsil chromatographic column ODS 3V (25 cm×4.6 mm) 5 microm and mobile phase – a mixture of 0.1 M potassium dihyd-

rogen phosphate buffer solution and acetonitrile (70:30, v/v), mobile phase rate – 1.0 ml/min, detection wavelength – 228 nm. The method was linear in the range of concentrations of bisoprolol fumarate 2.5–50 µg/ml and hydrochlorothiazide – 6.25–125 µg/ml. LOD – 0.01 µg/ml of both analytes. LOQ of bisoprolol – 0.03 µg/ml and hydrochlorothiazide – 0.05 µg/ml. The developed method has been successfully applied for the determination of bisoprolol fumarate and hydrochlorothiazide in drugs [16].

G. Arjun et al. described HPLC/UV method for the determination of bisoprolol in tablets using Gracesmart RP18 chromatography column, 5mcm (150 mm×4.6 mm) and mobile phase – a phosphate buffer solution pH 4.5 and acetonitrile (82:18, v/v), flow rate – 2.0 ml/min, wavelength of detection – 225 nm. The method was linear in the range of 50–500 µg/ml, correlation coefficient – 0.99921. The developed method has been successfully applied for the determination of bisoprolol fumarate in tablets [17].

Scientists E. Dinc, Z. C. Ertekin, G. Rouhani proposed UHPLC/UV method for the determination of bisoprolol and hydrochlorothiazide in tablets using experimental design 3³. Column temperature, mobile phase rate and 0.1 M N₃PO₄ percentage were chosen as investigating factors. The most suitable chromatographic conditions were the temperature of column – 58.2 °C, mobile phase rate – 0.37 ml/min and 23.6 % (0.1 M H₃PO₄). Total chromatography time was 0.6 min. Chromatography time of bisoprolol – 0.323 min, hydrochlorothiazide – 0.409 min. The method was linear in the range of concentrations of bisoprolol 8.0–40.0 µg/ml, hydrochlorothiazide – 2.0–26.0 µg/ml. One of the benefits of UHPLC/UV is rapidity that was illustrated as an example of the development of this method, which was used to determine bisoprolol fumarate and hydrochlorothiazide in tablets [19].

S. Kurbanoglu et al. developed UHPLC/UV method for the determination of bisoprolol and hydrochlorothiazide in drugs and biological fluids using chromatographic column Acquity UPLC BEH C18 1.7 µm (2.1×50 mm) and mobile phase – a mixture of acetonitrile and phosphate buffer solution pH 3.0, wavelength detection – 225 nm. The method was linear in the range of concentrations of bisoprolol 0.5–250 µg/ml, hydrochlorothiazide – 0.5–150 µg/ml, LOD and LOQ of bisoprolol was 0.07 µg/ml and 0.21 µg/ml, LOD and LOQ hydrochlorothiazide – 0.01 µg/ml and 0.03 µg/ml, respectively. The developed method has been successfully applied for the determination of bisoprolol and hydrochlorothiazide in tablets and urine [23].

Reverse-phase HPLC/UV method for the determination of bisoprolol and amlodipine in tablets was described by D. Vora and A. Kadav. The develop-

ped method uses a Luna C18-2 column (3 µ, 50×4.6 mm ID) and mobile phase – a mixture 25 mM of acetate buffer solution pH 5.0 and methanol (65:35, v/v), mobile phase rate – 0.8 ml/min, detection wavelength – 230 nm. Chromatography time of bisoprolol – 1.45 min, amlodipine – 3.91 min. The method was linear in the range of concentrations 8–33 µg/ml. The developed method was used to determine bisoprolol and amlodipine in drugs [24].

J. Bhatt et al. proposed HPLC/MS method for the determination of bisoprolol in blood plasma using the chromatography column Betabasic 8 column and internal standard – metoprolol. Total time of chromatography was 0.9 min. The developed method has been successfully applied for the determination of bisoprolol in blood plasma and the study of pharmacokinetics [26].

Gabriela Peste et al. developed HPLC/MS method for the determination of bisoprolol in blood plasma using a Zorbax SB-C18 Solvent Saver Plus chromatographic column, 3×100 mm, 3.5 µm and mobile phase – a mixture of 0.1 % formate acid pH 3 and acetonitrile (50:50, v/v) [27]. Chromatography time of bisoprolol was 1.7 min. The method was linear in the range of concentrations of 1–100 ng/ml, correlation coefficient – 0.99859. The developed method has been successfully applied for the determination of bisoprolol in blood plasma and the study of bioequivalence [28].

Reverse-phase HPLC/UV method for the determination of bisoprolol and metoprolol in blood plasma was described by A. J. Braza, P. Modamio, C. F. Lastra, E. L. Marino. In the developed method is used the chromatographic column Nucleosil C (18). Chromatography time of bisoprolol – 8.7 min, metoprolol – 3.2 min. The method was linear in the range of concentrations of both analysts 6.25–200 ng/ml. The developed method has been successfully applied for the determination of bisoprolol and metoprolol in blood plasma and the study of pharmacokinetics [29].

Scientists G. Hemavathi and S. M. Hipparagi proposed the bioanalytical method for the determination of bisoprolol and triamterene in blood plasma using the chromatographic column Welchrom XB C18, 50×4.6 mm, 5 µm, mobile phase – a mixture of 2 mM ammonium formate and acetonitrile (70:30, v/v) and internal standard – metoprolol, mobile phase rate – 0.60 ml/min. Total chromatography time was 3.5 min. Bisoprolol retention time – 2.57 min, triamterene retention time – 1.30 min. The method was linear in the range of concentrations of both analytes 2.04–210 ng/ml. The developed method has been successfully applied for the determination of bisoprolol and triamterene in blood plasma and the study of pharmacokinetics [30].

L. Ding et al. developed HPLC/MS method for the determination of bisoprolol in blood plasma using the chromatographic column ZORBAX SB-C18 and mobile phase – a mixture of 10 mM ammonium acetate buffer solution with addition of 0.1 % formic acid and acetonitrile (32:68, v/v). The total time of chromatography was 5 minutes. The method was linear in the range of concentrations of 0.05–120 ng/ml. The developed method was used to determine bisoprolol in blood plasma and to study bioequivalence [32].

G. Y. Liu et al. described HPLC/MS method for the determination of bisoprolol in plasma using the chromatography column Capcell Pak C (18) MG III column (100 mm x 2.0 mm, 5 microm) and internal standard – 5-bisoprolol isotope. The method was linear in the range of concentrations of 0.5–100 ng/ml. The developed method has been successfully applied for the determination of bisoprolol in blood plasma and the study of bioequivalence [33].

S. Li et al. proposed HPLC/MS method for the determination of antiarrhythmic drugs (diltiazem, amiodarone, propranolol, verapamil, bisoprolol, metoprolol, atenolol, and others) in blood plasma using the chromatographic column Capcell C (18) column (50 mm×2.0 mm, 5 microm) and mobile phase – a mixture of acetonitrile and water in gradient elution mode [35].

Prospects for further research. In light of the benefits discussed in this review, we can conclude that analysts are constantly working on developing new methods of analysis of bisoprolol in drugs and biological liquids and on their optimization in order to save time and consumables, which also ensures the efficiency of the developed methodology. Literature survey revealed that a number of methods have been reported for estimation of bisoprolol individually or in combination with other drugs. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC.

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО
МОЗ УКРАЇНИ

АНАЛІЗ ПІДХОДІВ ДО РОЗРОБКИ ТА ВАЛІДАЦІЇ МЕТОДІВ АНАЛІЗУ БІСОПРОЛОЛУ В ЛІКАРСЬКИХ ЗАСОБАХ І БІОЛОГІЧНИХ РІДИНАХ

Резюме

Вступ. Розробку аналітичної методики все більше впроваджують у фундаментальні фармацевтичні дослідження з урахуванням їх високої чутливості, точності, специфічності та виразності. Критерієм пошуку був аналітичний метод розробки бісопрололу. Огляд літератури проводили в період 1990–2018 рр., щоб зробити його оновленим та всеосяжним і показати нові підходи до розробки методів аналізу бісопрололу. Джерелами були всесвітньовідомі журнали, а ключовими словами в якості фільтра – бісопролол, розробка методів, валідація, спектрофотометрія, ВЕРХ, УВЕРХ. Даний огляд створено з метою зосередження на перевазі ВЕРХ. Однак існує дуже мало аналітичних методів для одночасного аналізу цих препаратів у комбінованій лікарській формі за допомогою ВЕРХ. Аналіз підходів до розробки методів аналізу бісопрололу в препаратах і біологічних рідинах показав, що ВЕРХ є найбільш придатним методом для аналізу бісопрололу в субстанціях, лікарських засобах, біологічних рідинах для проведення рутинного аналізу лікарських засобів, фармакокінетичних досліджень (біоеквівалентність *in vivo*), кінетики розчинення (біоеквівалентність *in vitro*, процедура Біовейвер).

Мета дослідження – проаналізувати підходи до розробки та валідації методів аналізу бісопрололу в лікарських засобах і біологічних рідинах.

Висновки. У світлі переваг, які обговорювали в цьому огляді, можна зробити висновок, що хіміки-аналітики постійно працюють над розробкою нових методів аналізу бісопрололу в лікарських засобах і біологічних рідинах та їх оптимізацією з метою економії часу і витратних матеріалів, що також забезпечує ефективність розробленої методології. Дослідження літератури показало, що для аналізу бісопрололу індивідуально або в комбінації з іншими лікарськими засобами існує ряд методів. Однак є дуже мало аналітичних методів, повідомлених для одночасного аналізу цих препаратів у комбінованій лікарській формі за допомогою ВЕРХ.

КЛЮЧОВІ СЛОВА: бісопролол; спектрофотометричний метод; вискоелективна рідинна хроматографія; кількісний аналіз; валідація.

АНАЛИЗ ПОДХОДОВ К РАЗРАБОТКЕ И ВАЛИДАЦИИ МЕТОДОВ АНАЛИЗА БИСОПРОЛОЛА В ЛЕКАРСТВЕННЫХ СРЕДСТВАХ И БИОЛОГИЧЕСКИХ ЖИДКОСТЯХ

Резюме

Вступление. Разработку аналитической методики все больше внедряют в фундаментальные фармацевтические исследования с учетом их высокой чувствительности, точности, специфичности и выразительности. Критерием поиска был аналитический метод разработки бисопролола. Обзор литературы проводили в период 1990–2018 гг., чтобы сделать его обновленным и всеобъемлющим и показать новые подходы к разработке методов анализа бисопролола. Источниками были всемирноизвестные журналы, а ключевыми словами в качестве фильтра – бисопролол, разработка методов, валидация, спектрофотометрия, ВЭЖХ, УВЭЖХ. Данный обзор создан с целью сосредоточения на превосходстве ВЭЖХ. Однако существует очень мало аналитических методов для одновременного анализа этих препаратов в комбинированной лекарственной форме с помощью ВЭЖХ. Анализ подходов к разработке методов анализа бисопролола в препаратах и биологических жидкостях показал, что ВЭЖХ является наиболее подходящим методом для анализа бисопролола в субстанциях, лекарственных средствах, биологических жидкостях для проведения рутинного анализа лекарственных средств, фармакокинетических исследований (биоэквивалентность *in vivo*), кинетики растворения (биоэквивалентность *in vitro*, процедура Биовейвер).

Цель исследования – проанализировать подходы к разработке и валидации методов анализа бисопролола в лекарственных средствах и биологических жидкостях.

Выводы. В свете преимуществ, которые обсуждали в этом обзоре, можно сделать вывод, что химики-аналитики постоянно работают над разработкой новых методов анализа бисопролола в лекарственных средствах и биологических жидкостях и их оптимизацией с целью экономии времени и расходных материалов, что также обеспечивает эффективность разработанной методологии. Исследование литературы показало, что для анализа бисопролола индивидуально или в комбинации с другими лекарственными средствами существует ряд методов. Однако очень мало аналитических методов, сообщенных для одновременного анализа этих препаратов в комбинированной лекарственной форме с помощью ВЭЖХ.

КЛЮЧЕВЫЕ СЛОВА: бисопролол; спектрофотометрический метод; высокоэффективная жидкостная хроматография; количественный анализ; валидация.

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