2024, 21(6): 2049-2060
https://doi.org/10.21123/bsj.2023.8223
P-ISSN: 2078-8665 - E-ISSN: 2411-7986
Baghdad Science Journal

Development and Validation of a Novel Analytical Method (Ion Pair HPLC) For Separating and Determining Bisoprolol Fumarate and Carvedilol in Pure and Their Pharmaceutical Forms.

Duaa Alhuseen*[1], Youssef Alahmad [1], Shoeb Alahmad [2]

[1]Department of Pharmaceutical Chemistry and Drug Control, Faculty of Pharmacy, AL- Baath University, Homs, Syria.
[2]Department of Pharmaceutical Chemistry and Drug Control, Faculty of Pharmacy, AL-Wataniya Private University, Hama, Syria.
* Corresponding author.

Received 13/12/2022, Revised 09/06/2023, Accepted 11/06/2023, Published Online First 20/11/2023, Published 1/6/2024

Abstract

This work shows a new analytical method (ion pair HPLC) for the analysis of Bisoprolol Fumarate (BIS) and Carvedilol (CAR) in bulk and tablet. The developed analytical method has been carried out on an Inertsil ODS-3 5µL column 4.6 X 250 mm (w), as stationary phase using a mobile phase {Acetonitrile/ water 50/50 (v/v) containing sodium heptane sulfonic salt 0.001M as Ion pair agent}. The detection wavelength was 223 nm and the flow rate was 1.5 mL /min. Retention times were 3.5 min of BIS and 5.8 min of CAR. The analytical method has been validated by ICH guidelines. The developed method gave linearity in the concentration range of 20–60 µg/ mL accuracy with mean recovery values between 98-102 % (99.73% for BIS and 101.2% for CAR). The developed method is useful for separating and determining Bisoprolol Fumarate and Carvedilol in their pharmaceutical forms.

Keywords: Bisoprolol Fumarate, Carvedilol, Determining, Ion Pair HPLC, Validation.

Introduction

Beta-blockers are used to treat cardiovascular diseases, tachycardia, congestive heart failure**,** and hypertension**.** Beta-blockers decrease blood pressure, including decrease renin and reduce cardiac output. Beta-blockers include propranolol, carvedilol, sotalol, labetalol, atenolol, bisoprolol, metoprolol, and esmolol[1].

Bisoprolol fumarate (1-[4-)[[2-Methyleethoxy)) (ethoxy] methyl]pphenoxy]-3[(methyl-ethyl)4{amino]-2-propeenol)-2-butenedioate[2], Fig.1, is a selective beta blocker, that is found in low therapeutic concentrations. The oral bioavailability of bisoprolol is 90%[3]. Various HPLC methods were applied to assay bisoprolol fumarate in pharmaceutical forms[4-6]. There were also UV-spectrophotometric methods to determine bisoprolol fumarate[7,8].

Carvedilol(CAR)1-(9H-carbazol-4yloxy)3[[2(2methoxyphenoxy)ethyl]amino]-,(±)-;(±)1(Carbazol4yloxy)3[[2(omethoxyphenoxy)ethyl]amino]2propanol[2] , Fig.1, is a β-adrenoceptor antagonist and is α_1-adrenergic blocker, it is also found in low therapeutic concentrations[9]. Various HPLC methods were applied to assay carvedilol in pharmaceutical forms[10,11]. There were also UV-spectrophotometric methods to determine carvedilol[12,13].

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All previous analytical methods were traditional spectroscopic and chromatographic methods. Therefore, the previous methods gave tailing peaks and bad resolution. In addition, they used toxic solvents such as methanol and depended on the use of buffer in mobile phase mixture.

The present research utilizes ion pair HPLC which improves separation efficiency and resolution factor and gives sharp peaks and reduces retention time without using toxic solvents. Therefore, it is an environmentally friendly method. With using ion pair reagent instead of buffer in mobile phase mixture to maintains safety of instrument and column and relieves pressure applied to them.

In this research, Ion pair HPLC has been used for the first time to separate and determine bisoprolol and carvedilol in pure and tablet. Ion pair is used to separate charged ionic compounds by binding with an ion pair reagent added to the mobile phase. This result in reducing polarity and getting its sharp peaks, and good separation. Ion pair HPLC is a new method to determine some drugs recently[14].

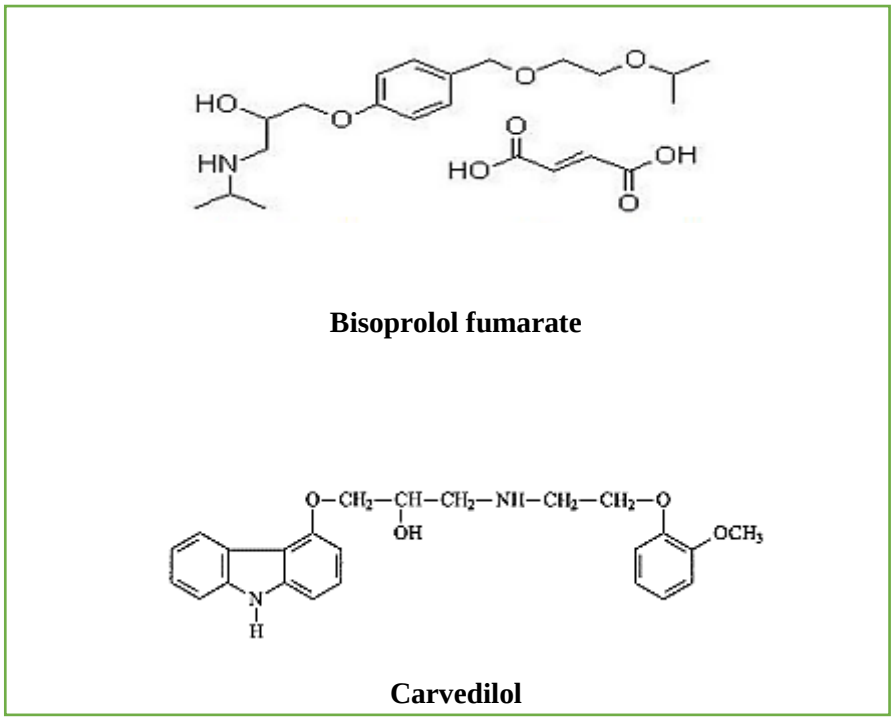

Figure 1. Chemical structure of Bisoprolol fumarate and Carvedilol[8].

Materials and Methods

Materials:
Standards substances of Bisoprolol fumarate (99.7%), and Carvedilol (99.5%) were provided by Emessa Pharmaceutical Industries, Homs Syria and Medico labs, Homs Syria, respectively. Acetonitrile (MERK, Germany), buffer (Monosodium phosphate), sodium heptane sulfonic salt (LOBA CHEMIE), deionized water and filters (0.45 µm).

Equipment:
The HPLC instrument: Prominence-I LC-2030C 3D shimadzu, with a UV detector (PDA); is connected to a PC (Lenovo ThinkPad X1 Carbon / Core i5/).

The ultrasonic bath model (JENEK / PS-80 A).

Analytical balance 0.0001 g (Sartorius).

Crison pH meter model TitroMatic 1S.

Pharmaceutical Formulations:
Bisocand tablets, Ultra medica, Damascus- Syria, labeled 2.5mg of Bisoprolol fumarate.

Bizocor tablets, Asia, Aleppo- Syria, labeled 2.5 mg of Bisoprolol fumarate.

Conofact tablets, Medico, Homs - Syria, labeled 2.5 mg of Bisoprolol fumarate.

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Concor cor tablets, MERK, have been purchased from Syria, labeled 2.5 mg Bisoprolol hemifumarate.

Carvedilol Emessa tablets, Emessa, Homs -syria, labeled Carvedilol 6.25 mg.

Cardivol tablets, Balsam, Homs - syria, labeled Carvedilol 6.25 mg.

Dilatrend tablets, Roche, have been purchased from Lebanon, labeled Carvedilol 6.25 mg.

Reference Solutions Preparation:

- Stock standard solutions of Bisoprolol fumarate, and Carvedilol were prepared by dissolving 25 mg of each drug in a mobile phase using a 50 mL volumetric flask, the content was dispersed under an ultrasonic bath for 15 min, to the substance was completely dissolved. Then, 5 mL of the solution was transferred to 50 mL calibrated flask and diluted by mobile phase; to give the final concentration (50µg/ mL).
- Working standard solutions were prepared by diluting the stock solutions to get the final concentrations between (20-60) µg/mL.

Tablets Solutions Preparation:

According to Pharmacopoeia, ten tablets were powdered; an amount equal to the labeled content (2.5 mg bisoprolol fumarate) was taken and dissolved in a volumetric flask (50 mL) containing a mobile phase. The content was sprinkled under magnetic stirring for 15 min and sonicated for10 min; to give the final concentration (50µg/ mL).

According to Pharmacopoeia, ten tablets were powdered; an amount equal to the labeled content (6.25 mg Carvedilol) was taken and dissolved in a volumetric flask (50 mL) containing mobile phase. The content was sprinkled under magnetic stirring for 15 min and sonicated for 10 min. Then 5 mL of the solution was transferred to a 25 mL calibrated flask and diluted by mobile phase; to give the final concentration (50µg/mL).

Results and discussion

Method Development and Optimization:

Several experiments were performed using an Inertsil® C18 reversed-phase column (4.6 mm x 250 mm) (5 µm particle size) and different mobile phase installations including different concentrations of (ion pair agent) until obtaining the ideal chromatographic peak. The optimum rate was chosen after conducting many experiments to get a symmetrical sharp peak with efficient separation, high resolution, and an appropriate retention time.

Initially, a mixture of acetonitrile: buffer in a ratio of 30:70 was used as the mobile phase. A good separation and the peaks were sharp and symmetrical, but with a long retention time {20 min for carvedilol}, Fig. 2.

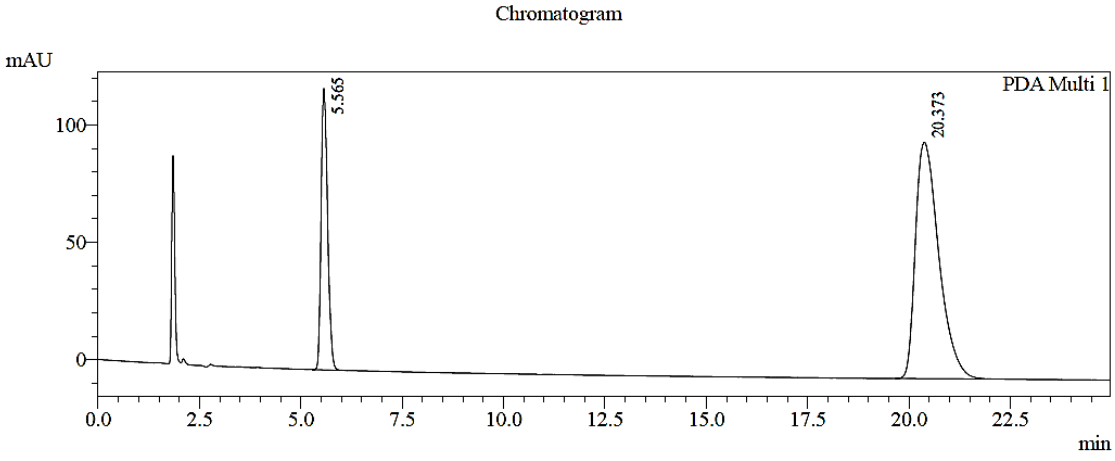

Figure 2. Bisoprolol fumarate and carvedilol chromatogram using mobile phase acetonitrile/buffer 30:70 v/v, (20µl injection, 50µg/mL of each drug).

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The mobile phase was modified, replacing the buffer with water (acetonitrile: water in a ratio of 30:70 containing sodium heptane sulfonic salt 0.001M as Ion pair agent.). Bad separation and overlapped peaks, Fig. 3.

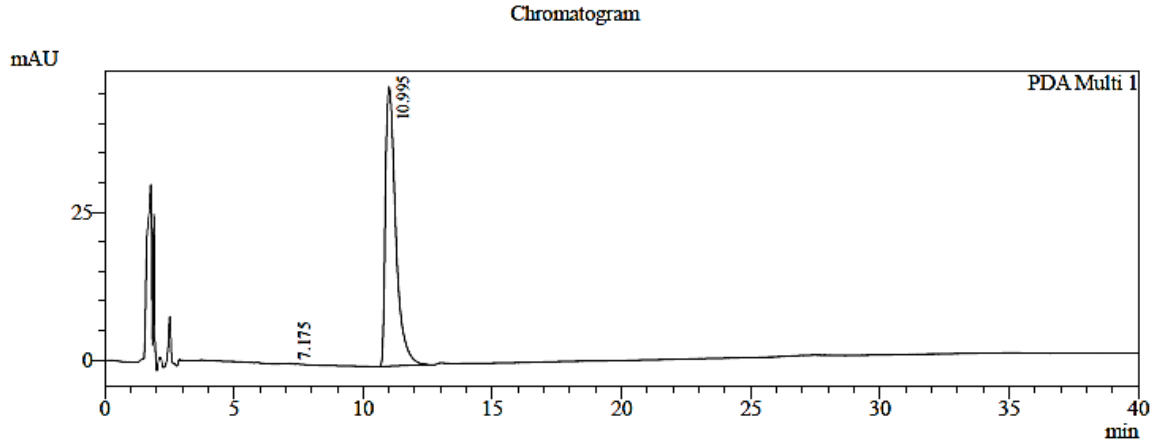

Figure 3. Bisoprolol fumarate and carvedilol chromatogram using mobile phase acetonitrile/ water 30:70 containing sodium heptane sulfonic salt 0.001M as Ion pair agent, (20µl injection, 50µg/mL of each drug).

The ratio of acetonitrile increased and the concentration the ion pair agent was decreased. (Acetonitrile: Water in a ratio of 50:50 containing sodium heptane sulfonic salt 10^{-5}M as Ion pair agent). Separation was bad with wide and overlapping peaks, Fig. 4.

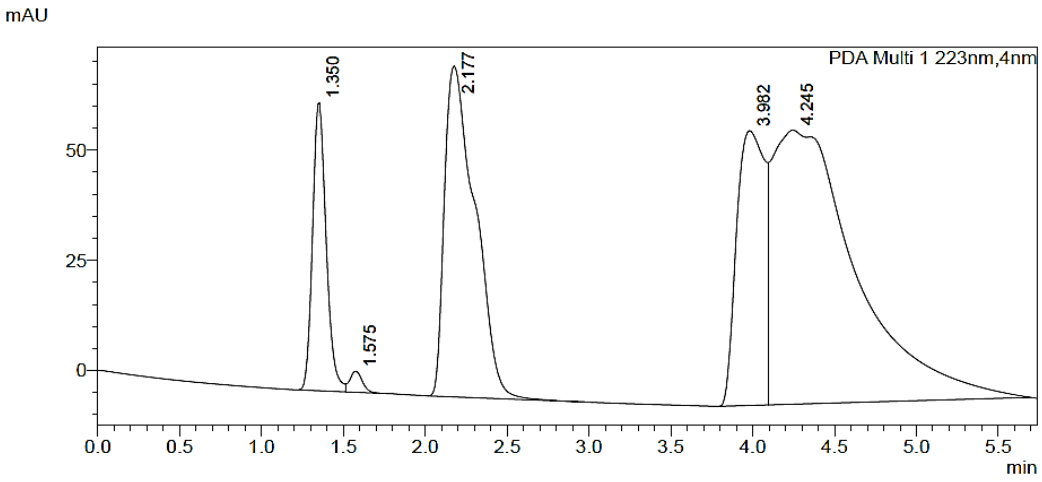

Figure 4. Bisoprolol fumarate and carvedilol chromatogram using mobile phase acetonitrile/Water 50:50 containing sodium heptane sulfonic salt 10^{-5} M as Ion pair agent, (20µl injection, 50µg/mL of each drug).

The ratio of the previous mobile phase was preserved and the concentration of (ion-pair agent)was increased (acetonitrile: water in a ratio of 50: 50 containing 0.001M sodium heptane sulfonic salt as ion pair agent). A good separation and the peaks are sharper and symmetrical with a short retention time. Fig. 5 shows the chromatogram under optimum conditions.

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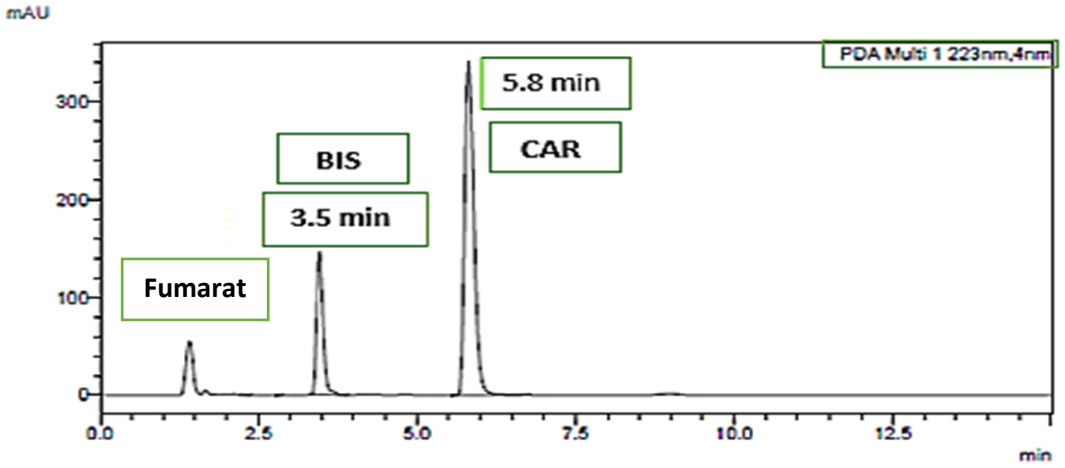

Figure 5. A. Bisoprolol fumarate and carvedilol chromatogram with optimum conditions, (20µl injection, 50µg/mL of each drug).

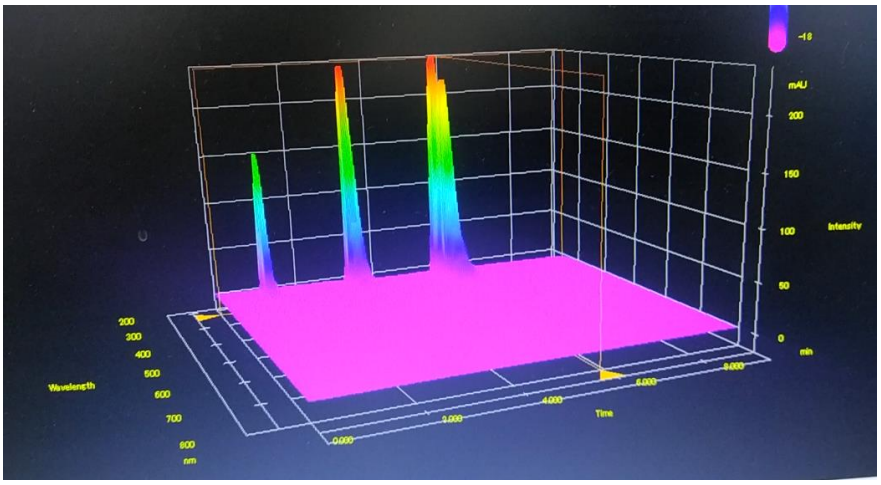

Figure 5. B. 3D chromatogram of Bisoprolol fumarate and carvedilol with optimum conditions, (20µl injection, 50µg/mL of each drug).

Optimum Conditions:

- The common wavelength of Bisoprolol fumarate and Carvedilol was 223 nm.
- An Inertsil® C18 reversed phase column ODS (4.6 mm x 250 mm) (5-µm particle size) was utilized.
- Mobile phase {Acetonitrile/ water 50/50 (v/v) contains sodium heptane sulfonic salt 0.001M as Ion pair agent}.

Analytical Method Validation:

The method has been validated according to the International Conference on Harmonization ICH[15-17].

Range:

The linearity has been demonstrated in the interval (20-60 µg/mL) for Bisoprolol fumarate and carvedilol.

Linearity:

Different concentrations of Bisoprolol fumarate were prepared (20, 30, 40, 50, 60) µg/mL Fig. 6, and the concentrations of carvedilol prepared were (20, 30, 40, 50, 60) µg/mL Fig. 7. The calculated correlation coefficients (R^2) were 0.9986 of BIS and 0.9997 of CAR. Therefore, the new method is linear.

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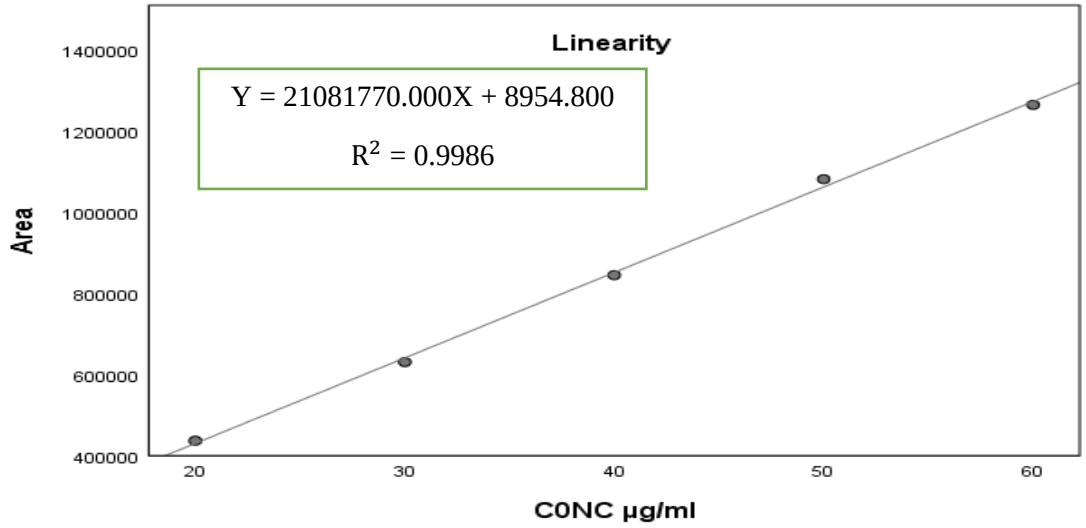

Figure 6. Linearity lines of Bisoprolol fumarate

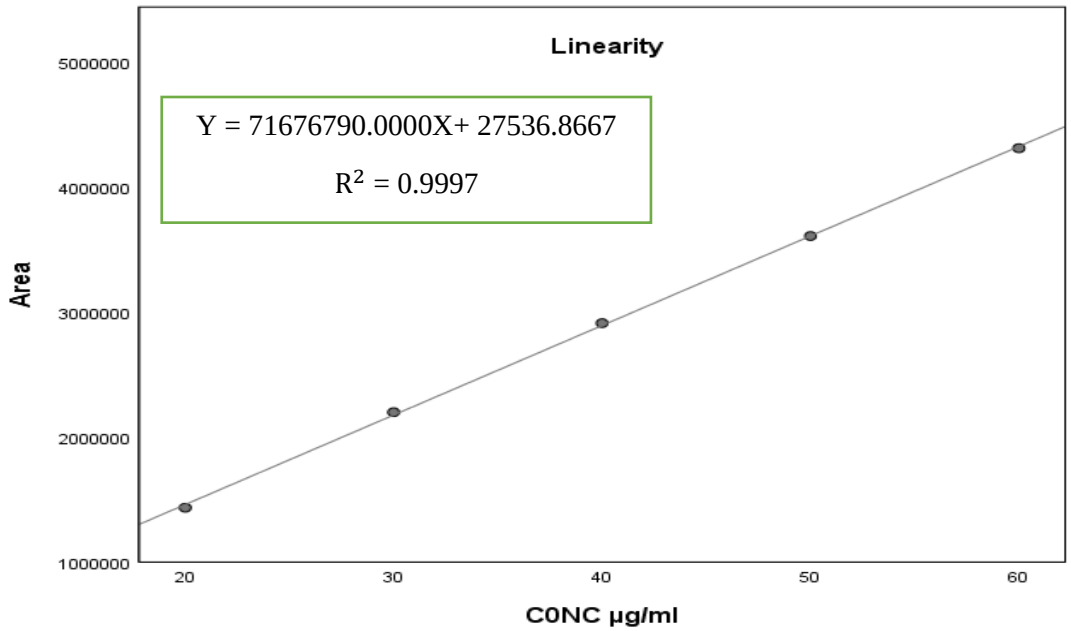

Figure 7. Linearity lines of carvedilol.

Accuracy:

Three concentration levels (40, 50, and 60 µg/mL) were used for accuracy. Mean recovery results for Bisoprolol fumarate (99.73%) and for carvedilol (101.2%) were between the acceptable range (98-102%) which indicates that the method is accurate and viable for determining BIS, and CAR Table 1.

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Table 1. Accuracy of the proposed method, Bisoprolol fumarate, Carvedilol.

Bisoprolol fumarate			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	39	0.210	99.02%
50	51	0.183	102%
60	58	1.293	98.19%
Mean recovery	99.73%		
Mean deviation	0.562		
Carvedilol			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	40	0.209	100%
50	51	0.129	102%
60	61	0.034	101.7%
Mean recovery	101.2%		
Mean deviation	0.124		

Precision:

Repeatability precision was performed by injecting six replicates of standard solution (50µg/mL) Bisoprolol fumarate, and (50µg/mL) Carvedilol, the results are shown in Table 2. Intermediate precision was determined by three replicate analyses of three concentration levels during three days. RSD % < 2%. Table 3.

Table 2. Repeatability precision for the proposed method.

Sample number 50 µg/mL	(Bisoprolol fumarate) Actual concentration	(Carvedilol) Actual concentration
1	54	51
2	53	50
3	53	50
4	53	50
5	53	50
6	53	51
Mean	53.1	50.3
RSD%	0.108	0.215

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Table 3. Intermediate precision for Method, Bisoprolol fumarate, Carvedilol.

Bisoprolol fumarate			
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	39	0.210	97.5%
50	51	0.183	102%
60	59	1.293	98.3%
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	39	0.118	97.5%
50	50	0.336	100%
60	61	0.421	101.6%
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	39	0.124	97.5%
50	49	0.650	98%
60	59	0.433	98.3%
Carvedilol			
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	41	0.209	102%
50	51	0.129	102%
60	61	0.034	101.6%
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	40	0.310	100.3%
50	50	0.791	100.9%
60	61	0.429	101.6%
Intra-day			
Theoretical Concentration (µg/mL)	**Actual concentration**	**RSD%**	**Recovery%**
40	39	0.166	99.5%
50	49	0.177	98.6%
60	60	0.567	100.4%

Sensitivity:

The sensitivity of the developed method was evaluated by LOQ and LOD. The calculated LOQ and LOD for Bisoprolol fumarate were 4µg/mL and 1µg/mL, respectively. Carvedilol were 3µg/mL and 1µg/mL, respectively.

Specificity:

The method specificity was assessed by retention times obtained from analyses of tablets. The retention times acquired by the developed analytical method were 3.5 and 5.8 min for BIS and CAR, respectively. This indicates no interference with the excipients. In addition, the areas of the peaks were compared with the standard chromatogram and were identical, Figs. 8, 9.

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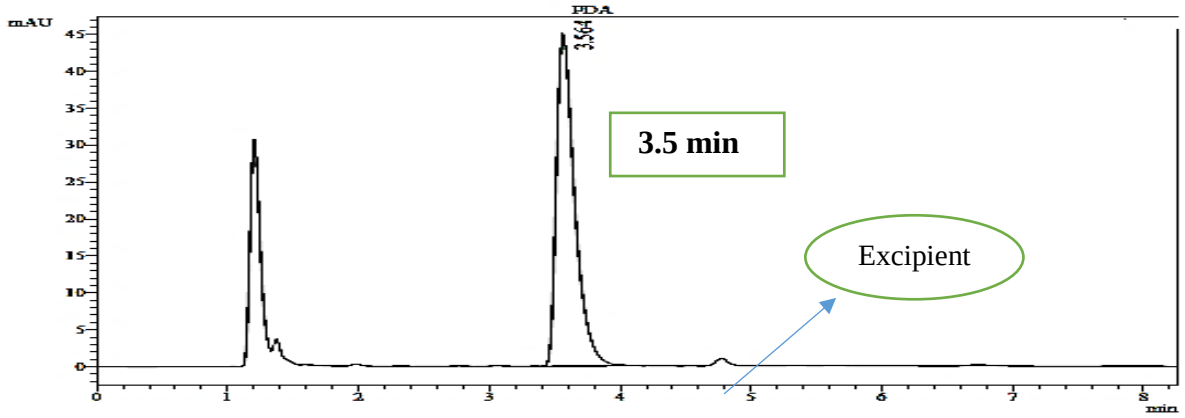

Figure 8. Chromatogram of the tablet solution of Bisoprolol fumarate (50µg/mL) under optimum conditions.

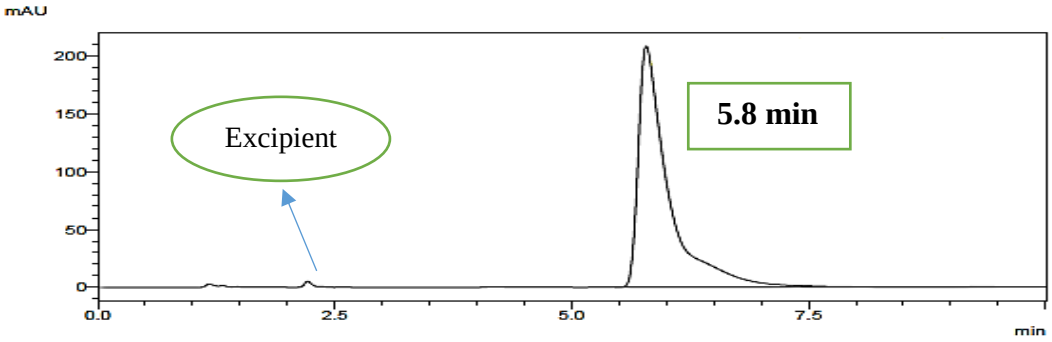

Figure 9. Chromatogram of the tablets solution of Carvedilol (50µg/mL) under optimum conditions.

Robustness:

The robustness was evaluated by changing in some chromatographic conditions, flow rate ±0.1, detection wavelength ±2 and mobile phase ratio ±2, respectively. RSD % was calculated between the developed condition and the changed condition, which prove that the developed method is robust at these changes, Table 4.

Table 4. Robustness for Method, Bisoprolol fumarate, Carvedilol.

	ratio	RSD%	Recovery%
Bisoprolol fumarate			
Flow rate (mg/min)	1.4	0.128	101%
	1.5	0.183	102.4%
	1.6	0.132	101%
Detection wavelength (nm)	221	0.356	100.3%
	223	0.183	102.4%
	225	0.711	102%
Mobile phase ratio	48/52	0.482	99.4%
	50/50	0.183	102.4%
	52/48	0.077	102%
Carvedilol			
	ratio	**RSD%**	**Recovery%**
Flow rate (mg/min)	1.4	0.883	102.3%
	1.5	0.791	100.9%
	1.6	0.744	102%
Detection wavelength (nm)	221	0.222	98%
	223	0.791	100.9%
	225	0.478	102.4%
Mobile phase ratio	48/52	0.159	98%
	50/50	0.791	100.9%
	52/48	0.134	102.3%

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Tablet forms Assay:

The developed method was applied to determine Bisoprolol fumarate and Carvedilol in tablets, and the results of quantitative analysis for Bisoprolol fumarate and Carvedilol were reported Table 5. All the tested formulations had concentrations within the specification, which recommended Bisoprolol fumarate tablets should contain not less than 90% and not more than 105% of the labeled amount[2], and not less than 90% and not more than 110% of the labeled amount for Carvedilol tablets[2].

Table 5. Results of Bisoprolol fumarate and Carvedilol tablets assay by the developed HPLC method.

Bisoprolol fumarate			
Formulation	**Claim (mg/tab)**	**Recovery**	**RSD%**
Bizocor	2.5	90.7%	0.05
Conofact	2.5	92%	0.07
Bisocand	2.5	92.7%	0.13
Concor cor	2.5	94%	0.01
Carvedilol			
Formulation	**Claim (mg/tab)**	**Recovery**	**RSD%**
Carvedilol	6.25	95%	0.78
Emessa	6.25	90.9%	0.16
Cardivol	6.25	98%	0.09
Dilatrend			

Conclusion

In this work, a new, simple, precise, robust, accurate and sensitive analytical method (ion-pair high-performance liquid chromatography) is developed and applied to determine bisoprolol fumarate and carvedilol in their tablet forms. This method could be an additional analytical technique in the routine quality control laboratory.

Acknowledgment

Faculty of Pharmacy, AL- Baath University, Medico labs, Editors & Reviewers efforts.

Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and Images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Authors signed an ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee at University of AL-Baath.

Author's Contribution

D. A. conducted all practical experiments, obtained readings and results, and presented them.
Y. A. undertook the general supervision of the research and the discussion of the obtained results and the method of presenting them.
S. A. supervised the design and organization of the practical side and supervised the implementation of experiments and obtaining results.

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2024, 21(6): 2049-2060
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P-ISSN: 2078-8665 - E-ISSN: 2411-7986
Baghdad Science Journal

تطوير وتقييم طريقة تحليلية جديدة (كروماتوغرافيا الزوج الشاردي عالية الأداء) للفصل والكشف عن البيزوبرولول فومارات والكارفيديلول في موادها الأولية وأشكالها الصيدلانية

دعاء الحسين[1]، يوسف الأحمد[1] وشعيب الأحمد[2]

[1]قسم الكيمياء الصيدلية والمراقبة الدوائية، كلية الصيدلة، جامعة البعث، حمص، سوريا.
[2]قسم الكيمياء الصيدلية والمراقبة الدوائية، كلية الصيدلة، الجامعة الوطنية الخاصة، حماة، سوريا.

الخلاصة

تم في هذا البحث تطوير طريقة كروماتواغرافيا سائلة عالية الأداء بتقنية الزوج الشاردي والتحقق من صلاحيتها لتحليل وكشف البيزوبرولول فومارات والكارفيديلول كمياً في موادها الأولية ومستحضراتها الصيدلانية، حيث تم استخدام كاشف الزوج الشاردي لأول مرة لهذا الغرض. تم اجراء التحليل الكروماتوغرافي للمواد الأولية باستخدام الشروط الكروماتوغرافية التالية: اسيتونتريل: ماء بنسبة 50:50 يحتوي على كاشف زوج شاردي (sodium heptane sulfonic salt 0.001M) كطور متحرك، وعمود كروماتوغرافي Inertsil ODS-3 5µm 4.6 X 250 mm، وكان طول الموجة المستخدم هو 223 نم، مع معدل التدفق 1.5 مل/د. أعطت الطريقة المطورة زمن احتباس قصير تحت هذه الشروط 3.5 دقيقة و5.8 دقيقة للبيزوبرولول فومارات والكارفيديلول على الترتيب، الأمر الذي يسمح بتحليل عدد أكبر من العينات ضمن زمن قصير نسبياً. قيمت صلاحية الطريقة وفقاً لتوصيات مؤتمر التوافق الدولي ICH. تم التحليل في مجال الخطية 20 – 60 مكغ/مل وكان متوسط قيم الاستردادية في اختبار الصحة ضمن المجال المقبول 98-102% (99.73% للبيزوبرولول و101.2% للكارفيديلول). إن الطريقة المطورة صالحة لتحديد ومعايرة وفصل البيزوبرولول فومارات والكارفيديلول بشكل دقيق ونوعي سواء كمواد أولية أو ضمن مستحضراتها الصيدلانية.

الكلمات المفتاحية: بيزوبروبولول فومارات، كارفيديلول، تحديد، كروماتوغرافيا الزوج الشاردي عالية الأداء، مصدوقية.