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СЪДЪРЖАНИЕ

Оригинални статии

<i>I. Манолов.</i> Синтез, структурни изследвания и свойства на някои производни на 4-хидроксикумарина.....	3
<i>A. Златков, B. Цветкова, Л. Андонова и П. Пейков.</i> Синтез, структурен анализ и определяне на лекарствено подобие на някои имидазолови производни.....	18
<i>M. Георгиева, A. Бижев и И. Ненчева.</i> Изолиране и характеризиране на пиролови хидразони с евентуална туберкулостатична активност. сравняване на методи за сепариране.....	26
<i>И. Манолов, Ч. Майхле-Мьосмер, E. Нике, Г. Момеков и X.-Ю. Махула.</i> Синтез, структура и цитотоксична активност на производно на 2-нитрофенилаланина.....	32
<i>B. Николова-Младенова, Г. Момеков и Д. Иванов.</i> Синтез на физикохимична характеристика на нов дериват на салицилалдехид бензол хидразона с висока цитотоксична активност.....	41
<i>Л. Пейкова, И. Пенчева, М. Манова и Г. Петрова.</i> Изследване с високоефективна течна хроматография на двойни и тройни смеси, съдържащи Venlafaxine, Citalopram, Sibutramine.....	45
<i>M. Манова, И. Пенчева, П. Пейков, Г. Петрова и B. Цветкова.</i> Валидиране на течнохроматографски метод за количествено определяне на HMG Co-A редуктазни инхибитори.....	50
<i>A. Тачев.</i> Бързи методи за количествено определяне на флавоноиди и танини в козметични продукти.....	55
<i>B. Костова, P. Попова и Д. Рачев.</i> Получаване и оптимизиране на матрични системи с включено лекарствено вещество със слабобазични свойства на база Kollidon® Sr.....	59
<i>C. Георгиева и Я. Колева.</i> Естрогенна активност на метаболитите на някои съединения, действащи върху ендокринната система.....	65
<i>C. Лазаров, P. Николов, A. Момчилова и E. Янев.</i> Ефекти на Nimesulide върху фосфолипидния състав на алвеоларния сърфактант при плъхове с модел на септичен респираторен дистрес синдром.....	77
<i>A. Стоименова, A. Савова, M. Манова, Г. Драганов, Г. Петрова и A. Златков.</i> Взаимодействия на Ginkgo biloba с лекарствени продукти.....	83
<i>E. Кожухарова, П. Михнев, Pier-Luigi Nimis.</i> Проектът „Ключ към природата” – интерактивно електронно пособие за изучаване и разпознаване на лечебни растения.....	91
<i>X. Лебанова, E. Григоров и И. Гетов.</i> Материовигиланс – основни понятия и законодателна рамка.....	98
<i>B. Кирилов, E. Григоров и И. Гетов.</i> Проучване на приложението на витамини с антиоксидантни свойства и анализ на пазара в България.....	104
Обзори	
<i>Д. Обрешкова.</i> Аналитично проучване и качествен контрол на български продукти от растителен произход с антиоксидантна активност.....	108
Инструкции към авторите	115

CONTENTS

Original articles

<i>I. Manolov.</i> Synthesis, structure investigations and properties of some 4-hydroxycoumarin derivatives.....	3
<i>Al. Zlatkov, B. Tsvetkova, L. Andonova and P. Peykov.</i> Synthesis, structural analysis and drug-likeness estimation of some imidazole derivatives.....	18
<i>M. Georgieva, A. Bijev and I. Nenchewa.</i> Isolation and characterization of isomers of pyrrole-hydrazones with possible tuberculostatic activity. comparison of methods for separation.....	26
<i>I. Manolov, C. Maichle-Mössmer, E. Niquet, G. Momekov and H.-J. Machulla.</i> Synthesis, structure and cytotoxic activity of a 2-nitrophenylalanine derivative.....	32
<i>B. Nikolova-Mladenova, G. Momekov and D. Ivanov.</i> Synthesis and physicochemical characterization of new salicylaldehyde benzoyl hydrazone derivative with high cytotoxic activity.....	41
<i>L. Peykova, I. Pencheva, M. Manova and G. Petrova.</i> HPLC study of binary and triple mixtures containing venlafaxine, citalopram and sibutramine.....	45
<i>M. Manova, I. Pencheva, P. Peikov, G. Petrova and B. Tsvetkova.</i> Validation of hplc method for determination of HMG Co-A reductase inhibitors.....	50
<i>A. Tachev.</i> Rapid methods for quantitation of flavonoids and tannins in cosmetic products.....	55
<i>B. Kostova, R. Popova and D. Rachev.</i> Obtaining and optimization of matrix systems which contain drug with weak basic properties based on Kollidon® SR.....	59
<i>S. Georgieva and Y. Koleva.</i> Metabolic estrogenic activity of some endocrine disruptor chemicals.....	65
<i>S. Lazarov, R. Nikolov, A. Momtchilova and E. Yanev.</i> Effects of nimesulide on the phospholipid composition of the alveolar surfactant in rats with model of the septic respiratory distress syndrome.....	77
<i>A. Stoimenova, A. Savova, M. Manova, G. Draganov, G. Petrova and A. Zlatkov.</i> Medicine interactions with Ginkgo biloba.....	83
<i>E. Kozuharova, P. Mihnev and Pier-Luigi Nimis.</i> The Key-to-Nature Project – interactive e-tool for studying and identification of medicinal plants.....	91
<i>H. Lebanova, E. Grigorov and I. Getov.</i> Materiovigilance – Basic Concepts And Legislative Framework.....	98
<i>B. Kirilov, E. Grigorov and I. Getov.</i> Study on the use of antioxidant vitamins on the bulgarian market.....	104
Reviews	
<i>D. Obreshkova.</i> Analytical study and quality control of bulgarian drugs with antioxidant activity.....	108
Instructions To Authors	118

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VALIDATION OF HPLC METHOD FOR DETERMINATION OF HMG CO-A REDUCTASE INHIBITORS

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Summary. The goal of the present study is an adaptation and validation of the Pharmacopoeia HPLC method for evaluation of HMG-Co A reductase inhibitors. In adaptation, mobile phase and chromatographic column are modified. The analytical procedure is validated with respect to specificity, linearity, precision, accuracy, robustness and LOD and LOQ. The proposed RP-LC method can be applied for the routine analysis of commercially available formulations of simvastatin and lovastatin.

Key words: HPLC, validation, simvastatin, lovastatin

ВАЛИДИРАНЕ НА ТЕЧНОХРОМАТОГРАФСКИ МЕТОД ЗА КОЛИЧЕСТВЕНО ОПРЕДЕЛЯНЕ НА HMG CO-A РЕДУКТАЗНИ ИНХИБИТОРИ

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Резюме. Проведени са изследвания с цел адаптиране и валидиране на фармакопееен течнохроматографски метод за анализ на HMG-Co A-редуктазни инхибитори, като са модифицирани две от хроматографските условия – съставът на подвижната фаза и видът на сорбента. Методът е валидиран по отношение на специфичност, линейност, точност, повторемост, устойчивост, граница на количествено определяне и граница на откриване. Аналитичната процедура е приложена успешно за количествено определяне на Simvastatin и Lovastatin в таблетки.

Ключови думи: HPLC, валидиране, simvastatin, lovastatin

Introduction

Hypercholesterolemia is one of the major risk factors for coronary heart disease [1]. Therapeutic strategies for the prevention of atherosclerosis are essentially based on the correction of major risk factors, such as elevated plasma lipid levels or arterial blood pressure [11]. In the recent years, a new class of agents was developed that specifically inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. A number of clinical studies have demonstrated that HMG-CoA reductase inhibitors, either alone or in association with other hypolipidemic drugs, can induce regression of vascular atherosclerosis, decrease the incidence of coronary heart disease, and improve survival in coronary heart disease patients [4, 15, 18, 20]. After the discovery of the first INN of HMG Co-A reductase inhibitors, simvastatin and lovastatin, their market share performs permanent

increase and they became of a major interest for all pharmaceutical manufacturers [14]. For the first authorized INN, a pharmacopoeial method for their analytical assay is already available [5]. The analytical methods used for quality control of HMG Co-A reductase inhibitors are in general HPLC methods [5]. The development of lots of new INN of HMG Co-A reductase inhibitors with well established chemical and pharmacological characteristics pose a task for the adaptation of the existing pharmacopoeia methods for HMG Co-A reductase inhibitors' simultaneous analytical characterization. This is especially important for the generic pharmaceutical manufacturers to be able quickly to prepare the marketing authorisation dossier, after the patent expiration, and to benefit from the provision of the European medicinal legislation [6].

Researches are trying either to develop new HPLC methods or to adapt the pharmacopoeia one. Borek - Dohalský et al. are using the HPLC method

for quantitative determination of the major statin drug atorvastatin (ATV) and its metabolite 2-hydroxyatorvastatin (HATV) [2]. For the pharmacokinetic purposes prevail the studies that are using the liquid chromatography alone or in combination with mass spectrometry for the determination of HMG Co-A reductase inhibitors in human plasma [3, 7-10, 19, 22]. The HPLC was used also for the stability monitoring of lovastatin [12].

Of a particular interest are the articles focusing on the usage of HPLC for the simultaneous analysis of HMG Co-A reductase inhibitors or for their determination in pharmaceutical dosage forms. These studies were performed for amlodipin and atorvastatin by Sivakumar et al. [16]. Stanisz et al. validated the HPLC method for the determination of atorvastatin in tablets and for monitoring stability in solid phase [17]. Wang and co-workers applied the UV-spectrometric for determination of simvastatin in its tablet dosage form [21]. It was found only one work for the simultaneous analysis of five HMG-CoA reductase inhibitors – atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin – Pasha et al. develop a new method for use in pharmaceutical formulations [13]. This stimulated our interest towards the adaptation of Pharmacopoeia method for simultaneous analytical assay of HMG Co-A reductase inhibitors substances, as well as in pharmaceutical dosage forms.

The goal of this study is an adaptation and validation of the Pharmacopoeia HPLC method for determination of lovastatin and simvastatin in tablet formulations.

Materials and methods

Reagents

Simvastatin and lovastatin pure powder with 99.87 and 99.50 % purity were used as standards. Tablets containing 40 mg active drugs were obtained commercially. LC-grade acetonitrile was supplied from Merck (Germany). All other chemical reagents were of analytical grade.

Instrumentation and chromatographic conditions

Chromatography is carried out isocratically, on modular HPLC system LC-10A Shimadzu (Japan) arranged with a LC-10A pump, solvent degasser DGU-3A, Rheodyne injector with 20 ml loop, column oven CTO-10A, SPD-M10A diode array detector and communication bus module CBM-10A. Compounds are separated on a LiChrosorb C18, 250 mm x 4.6 mm, 5 µm column. The mobile

phase is 70:30 (v/v) mixture of water and acetonitrile, filtered and degassed prior to use. Isocratic elution is carried out at a flow rate of 1.5 ml/min at ambient temperature. UV-detection is performed at 240 nm.

Preparation of reference solutions

Stock solutions of simvastatin and lovastatin were prepared at 200 µg/ml in mobile phase as a diluent. The working solution of simvastatin and lovastatin was prepared at concentration of 40.00 µg/ml, respectively, by diluting the stock solutions in mobile phase.

Preparation of test preparation

Ten tablets were weighed and finely powdered. An accurately weighed amount of the powder equivalent to average mass of one tablet was transferred into a 100.0 mL volumetric flask. Approximately 70 mL of mobile phase were added, sonicated for 10 min and shaken for 15 min. The volume was diluted to the mark with mobile phase and mixed thoroughly. The solution was filtered through a 0.45 µm membrane filter and was further diluted with mobile phase to achieve a final concentration of 40.00 µg/ml.

Results and discussion

The mobile phase consisted only of acetonitrile and water without buffers and the retention times of all HMG-Co A reductase- inhibitors do not exceed 10 minutes. Isocratic regime permits to obtain a good chromatographic behavior in parallel of linear gradient, buffered phases and ion-pair techniques presented in Pharmacopoeia and other literature sources.

Validation of HPLC method

In order to prove the reliability of the method, the procedure was validated by investigating the analytical parameters selectivity, linearity, precision, accuracy, robustness, limit of detection (LOD) and limit of quantitation (LOQ). Validation characteristics are in conformity with the requirements of EU Pharmacopoeia VI [8].

Specificity

The specificity of the method was determined by checking the interference with the components from placebo. No interference was observed for any of the components like excipients of both drugs.

Linearity

For determination of the linearity, a set of solutions of substances with increasing concentration was

prepared and analysed by linear regressive analysis. Linear correlation was obtained between peak area and concentration in the range of 4-24 mg/ml for simvastatin and 6-32 mg/ml for lovastatin. The corresponding correlation coefficients (R^2) were 0.9998 and 0.9996 for simvastatin and lovastatin, respectively. An excellent correlation existed between the peak areas and concentration of both compounds.

Precision

The precision of the method, as intra-day repeatability, was evaluated by performing six independent assays of the test sample preparation and calculating RSD (%). The intermediate (inter-day) precision of the method was checked by performing same procedure on different days by another person under the same experimental conditions.

The RSD values measured during assessment of intraday and interday precision were < 2.0% for both simvastatin and lovastatin, confirming the method is precise (Table 1).

Accuracy

For determination of the accuracy, samples of model mixtures placebo with adding active ingredient with content of 80% to 120% of theoretical quantity were analysed. Each sample was analysed in triplicate. Values of SD and RSD are

within the pharmacopoeia limits. The results for the accuracy investigations are shown in Table 2, presented as % recovery and RSD.

Robustness

The robustness of the method is a measure of the capacity to remain unaffected by small variations in method parameters and provides indication of its reliability during normal usage. Robustness of the analytical procedure was studied by deliberately varying parameters like mobile phase composition and flow rate. Column-to-column reproducibility was also checked by using a C18 column of different make (Nucleosil) with same dimension.

The elution order and resolution for both components were not significantly affected by small variation of the conditions. Results from study of the robustness of the method were listed in Table 3.

Limit of detection and limit of quantification

The limits of detection and quantification were evaluated by serial dilution of simvastatin and lovastatin stock solution until the signal-to-noise ratios were 3:1 for LOD and 10:1 for LOQ. The LOD for simvastatin and lovastatin were 25.00 and 30.00 μg , respectively; the LOQ were 50.00 and 70.00 μg , respectively.

Table 1. Precision of the method proposed

Simvastatin			Lovastatin		
Amount claimed (mg/tablet)	Amount found (mg/tablet)		Amount claimed (mg/tablet)	Amount found (mg/tablet)	
	Intra-day repeatability	Inter-day repeatability		Intra-day repeatability	Inter-day repeatability
40.00	39.95	39.58	40.00	39.54	39.51
	38.96	39.46		39.47	39.62
	39.24	39.05		39.87	39.80
	39.51	39.02		39.12	39.26
	38.99	39.87		39.56	39.18
	39.12	39.65		39.14	39.71
Mean	39.26	39.43	Mean	39.45	39.51
S_d	0.378	0.339	S_d	0.284	0.248
%RSD	0.96	0.86	%RSD	0.72	0.68

Table 2. Accuracy of the method described

Simvastatin			Lovastatin		
Added amount, mg	Found amount, mg	Recovery, %	Added amount, mg	Found amount, mg	Recovery, %
32.00	31.91	99.72	32.00	31.76	99.25
	31.82	99.43		31.91	99.72
	32.01	100.0		31.82	99.43
40.00	39.34	98.35	40.00	39.52	98.80
	39.68	99.20		39.68	99.20
	39.73	99.32		39.51	98.77
48.00	48.10	100.2	48.00	48.00	100.0
	47.74	99.46		47.59	99.15
	47.56	99.08		47.82	99.63
Mean: 99.42 S _d = 0.543 RSD (%) = 0.55			Mean: 99.32 S _d = 0.411 RSD (%) = 0.41		

Table 3. Robustness parameters of LC method (n=6)

Factor	Level	Simvastatin		Lovastatin	
		Assay, %	% RSD	Assay, %	% RSD
Mobile phase composition 65:35 70:30 75:25	-5	100.0	0.65	98.8	0.98
	0	99.6	0.93	99.6	1.05
	+5	99.4	0.92	99.1	0.87
Flow rate of mobile phase 1.3 1.5 1.7	-0.2	98.7	0.64	98.2	0.56
	0	101.0	0.89	99.6	0.85
	+0.2	99.8	0.97	99.8	1.21
Stationary phase Nucleosil C 18 LiChrosorb C18	-	99.8	0.91	99.1	1.04
	-	99.5	0.98	99.6	0.95

Conclusion

An adapted and validated pharmacopoeia method for determination of simvastatin and lovastatin was developed as well as mobile and stationary phase were modified. The proposed method is simple, selective and applicable for routine analysis of HMG-CoA reductase inhibitors in pharmaceutical preparations.

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