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КОНТРОЛЬ СЕЛЕКТИВНОСТИ РАЗДЕЛЕНИЯ ДИКОФЕОИЛХИННЫХ КИСЛОТ В ОБРАЩЕННО-ФАЗОВОЙ ВЭЖХ С β-ЦИКЛОДЕКСТРИНОМ В ПОДВИЖНОЙ ФАЗЕ

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В работе исследовано изменение селективности разделения хлорогеновых (моно- и дикофеоилхинных) кислот в условиях обращенно-фазовой ВЭЖХ при добавлении β-циклодекстрина в подвижную фазу. Как известно, добавление β-циклодекстрина в подвижную фазу может приводить к модификации стационарной подвижной фазы. Для исключения влияния in situ модификации стационарной фазы циклодекстрином обычная С18 фаза была заменена на С4 фазу. Установлено, что по мере увеличения концентрации β-циклодекстрина в подвижной фазе удерживание всех моно- и дикофеоилхинных кислот уменьшается вследствие образования в подвижной фазе комплексов включения. При этом уменьшение времен удерживания не одинаково для всех исследованных изомеров, что указывает на различные значения констант комплексообразования "гость-хозяин". Предложенная в работе упрощенная схема расчета констант комплексообразования с учетом возможного образования комплексов состава 1:2 позволила рассчитать константы для монокофеоилхинных кислот и сумму констант возможных изомерных комплексов состава 1:1 для дикофеоилхинных кислот и показала, что образование комплексов состава 1:2 маловероятно. Показано, что качественно сумма констант для дикофеоилхинных кислот коррелирует с константами для соответствующих монокофеоилхинных кислот, но с учетом стерических затруднений образования комплексов включения 1:1 для дикофеоилхинных кислот. Для качественной оценки стерических препятствий использовали анализ некоторых оптимизированных методом AM1 в пакете HyperChem 8.0.8 конформаций дикофеоилхинных кислот и комплекса включения 4-кофеоилхинной кислоты в β-циклодекстрин.

Ключевые слова: комплексы включения "гость-хозяин", хлорогеновые кислоты, β-циклодекстрин, обращенно-фазовая ВЭЖХ, подвижная фаза

SELECTIVITY CONTROL OF DICAFFEOYLQUINIC ACIDS SEPARATION IN REVERSED-PHASE HPLC WITH β-CYCLODEXTRINE IN A MOBILE PHASE

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The paper investigates the change in the separation selectivity of the chlorogenic (mono- and dicaffeoylquinic) acids under conditions of reverse-phase HPLC with the addition of β-cyclodextrin into the mobile phase. To exclude the effect of in situ modification of the stationary phase by cy-

clodextrin, the usual C18 phase was replaced by the C4 phase. It was found that as the concentration of β-cyclodextrin in the mobile phase increases, the retention of all mono- and dicaffeoylquinic acids decreases due to the formation of inclusion complexes in the mobile phase. At the same time, the decrease in retention times is not the same for all the studied isomers, which indicates different values of the constants of the "host-guest" complex formation. The simplified scheme proposed in the paper for calculating the constants of complexation, taking into account the possible formation of complexes of composition 2: 1, allowed us to calculate the constants for monocaffeoylquinic acids and the sum of the constants of possible isomeric compounds of composition 1:1 for dicaffeoylquinic acids and showed that the formation of complexes of composition 2:1 is unlikely. It is shown that qualitatively the sum of the constants for dicaffeoylquinic acids correlates with the constants for the corresponding monocaffeoylquinic acids, but taking into account the steric restrictions in the formation of 1:1 inclusion complexes for dicaffeoylquinic acids. For a qualitative assessment of steric restrictions, the analysis of some conformations of dicaffeiolquinic acids optimized by the AM1 method in the HyperChem 8.0.8 package and the complex of inclusion of 4-caffeoylquinic acid in β-cyclodextrin was used.

Key words: "host-guest" inclusion complexes, chlorogenic acids, β-cyclodextrin, reversed-phase HPLC, mobile phase

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INTRODUCTION

There may arise a problem in separation of the three common isomers of caffeoylquinic acids: 3-caffeoylquinic (neochlorogenic, 3CQA), 5-caffeoylquinic (chlorogenic, 5CQA) and 4-caffeoylquinic (cryptochlorogenic, 4CQA) acids in reversed-phase HPLC [1] because of close structures of the substances. The problem may be solved by utilization of cyclodextrins added to mobile phase due to inclusion "host-guest" complex formation in the case of different constants of complexation for compounds to be separated [2, 3]. Meanwhile the dependence of solute retention on concentration of cyclodextrin in a mobile phase allows to calculate values of complex formation constant [2-5]. Formation of "quest-host" complexes with cyclodextrins as host molecules can induce modification of physicochemical properties of guest molecules by enhancing water solubility as well as stability in solution [6-8] and bioavailability [9].

In spite of great value of chlorogenic acids isomers as secondary plant metabolites and as high potency antioxidants "quest-host" complexes of cyclodextrins except for the paper [2] were intensively studied only for 5CQA (2, 10-14]) and the only one publication related with 3CQA was found [15]. Moreover, for dicaffeoylquinic acids (diCQAs) no papers about "quest-host" complexes with cyclodextrins are available for us. There is a lot of publications about determination of diCQAs in different plant sources, but we were unable to find papers devoted to investigation of chromatographic behavior of diCQAs in reversed-phase HPLC as well as in the case of mobile phase modification with cyclodextrins.

Thus the objective of this study was to determine the regularities of diCQAs chromatographic behavior in reversed-phase HPLC with addition of β-cyclodextrin into a mobile phase as a consequence of different values of "host-guest" complexes constants.

EXPERIMENTAL TECHNIQUES

Chlorogenic acids were extracted by maceration of mate tea (dried leaves of *Ilex paraquariensis*) in boiling water. After cooling the infusion chlorogenic acids were cleaned-up by solid phase extraction on syringe cartridges Diapack C18 (BioChemMack ST, RF). The re-extract in 30 vol. % of acetonitrile and 0.75 vol. % of *ortho*-phosphoric acid in water was dilutes by the water (1:2 by volume), filtered through syringe filter (0.45 μm) before direct injection into chromatographic system.

Separations were performed on an Agilent 1200 Infinity chromatograph with a diode array detector. A chromatographic column 150×4.6 mm Kromasil

300-5C4 was used, column thermostat temperature was 30 °C. Chromatograms were recorded and processed using the ChemStation software. Solutes were identified by electronic absorption spectra (with λ_{max} near 235 nm and characteristic shoulder at ~295 nm) and chromatographic behavior compared to literature data [16-19]. 5-caffoylquinic acid hemihydrate (SIGMA-ALDRICH, India) was used as standard solute.

The mobile phases were prepared using acetonitrile of HPLC Gradient grade (Fisher Chemical, Germany), *ortho*-phosphoric acid (85%, RUSHIM), distilled water and β-cyclodextrin (KLEPTOSE®).

RESULTS AND DISCUSSION

To escape stationary phase modification *in situ* by cyclodextrin from the mobile phase [20] we used C4 column instead of commonly used C18 column. Among coffee [20] and mate [16-17] infusion according to our data in the latter case mole fraction of dicaffeoylquinic acids is greater. Moreover in this case there is no feruloyl acid derivatives that complicates chromatogram, thus namely mate was used for further investigation.

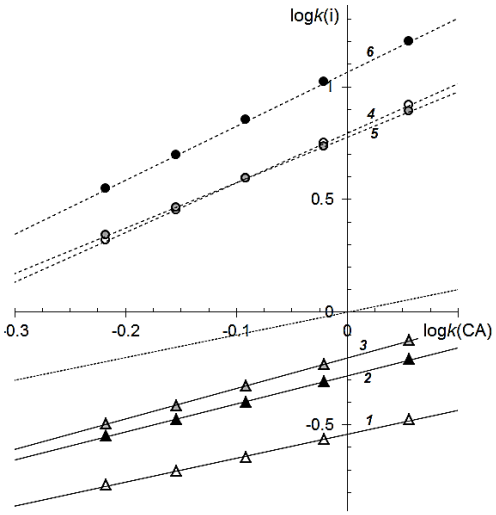

Fig. 1. Relative retention of mono- and dicaffeoyl acids vs retention of caffeic acid. Column 150×4.6 mm Kromasil 300-5C4, mobile phases 0.25 vol.% of ortho-phosphoric acid and 12 – 14 vol. % of acetonitrile in water; 30ºC. Compounds 1 – 3CQA; 2 – 5CQA, 3 – 4CQA, 4 – 3,4diCQA; 5 – 3,5diCQA and 6 – 4,5diCQA; dotted line – for reference substance – caffeine acid (CA)

Рис. 1. Относительное удержание моно- и дикаффеоиловых кислот по сравнению с удержанием кофейной кислоты. Колонка 150×4,6 мм Kromasil 300-5C4, подвижные фазы 0,25 об.% ортофосфорной кислоты и 12-14 об. % ацетонитрила в воде; 30 °C. Соединения 1 – 3CQA; 2 – 5CQA, 3 – 4CQA, 4 – 3,4diCQA; 5 – 3,5diCQA и 6 – 4,5diCQA; пунктирная линия – для эталонного вещества – кофеиновая кислота (CA)

In the plant leaves three of four monocaffeoylquinic acids are synthesized – 3CQA, 4CQA and 5CQA as well as three possible corresponding combination of substitution in quinic acid resulted in dicaffeoylquinic acids isomers: 3,5diCQA, 3,4diCQA and 4,5diCQA. All of monocaffeoylquinic acids are separated in the mobile phases containing 0.25 vol. % of *ortho*-phosphoric acid and from 12 to 14 vol. % of acetonitrile in water though separation of 4CQA and 5CQA is highly desirable to be improved. Meanwhile among dicaffeoylquinic acids 4,5DiCQA has the greatest retention while 3,4diCQA and 3,5diCQA are eluted closely becoming a problem pair for the separation, Fig. 1.

The mobile phase composition taken for the investigation (0.25 vol. % of *ortho*-phosphoric acid and 12% of acetonitrile in water) permits even separation of 3,4diCQA and 3,5diCQA, though large retention time of 4,5diCQA (about 40 min) makes this conditions not suitable for serial analysis. Meanwhie addition of β-cyclodextrine into a mobile phase markedly alters the chromatograms and solutes resolution, Fig. 2.

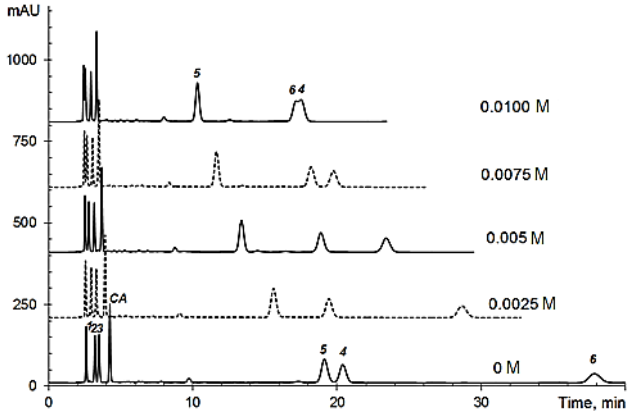

Fig. 2. Alteration of solute separation selectivity at a rise of β-cyclodextrin concentration in a mobile phase. Column 150×4.6 mm Kromasil 300-5C4, mobile phases 0.25 vol.% of ortho-phosphoric acid and 12. % of acetonitrile in water, β-cyclodextrin concentrations are pointed on chromatograms; 30 ºC. Compounds 1 – 3CQA; 2 – 5CQA, 3 – 4CQA, 4 – 3,4diCQA; 5 – 3,5diCQA and 6 – 4,5diCQA

Рис. 2. Изменение селективности разделения растворенных веществ при повышении концентрации β-циклодекстрина в подвижной фазе.Колонка 150×4,6 мм Kromasil 300-5C4, подвижные фазы 0,25 об.% ортофосфорной кислоты и 12% ацетонитрила в воде, концентрации β-циклодекстрина указаны на хроматограммах; 30 °C. Соединения 1 - 3CQA; 2 – 5CQA, 3 – 4CQA, 4 – 3,4CQA; 5 – 3,5diCQA и 6 – 4,5diCQA

According to presented data the retention of 4,5diCQA decreases the most highly when the concentration of β-cyclodextrin rises from 0 to 0.01 M. The decrease is also high for 3,5diCQA, while the retention 3,4diCQA changes slowly. This is the consequence of decrease of "host-guest" complexes formation constants (K) in series:

K(3,4diCQA) < K(3,5diCQA) < K(4,5diCQA).

For dicaffeoylqunic acids formation of "host-guest" complexes with β-cyclodextrin in ratio 2:1 may

be proposed if there are no sterically restriction for the formation.

Let us take some of the diCQAs isomer, that have caffeic acid substituents in quinic acid positions *i* and *j*. If in a mobile phase appears β-cyclodextrin two types of complexes may be formed of a simple 1:1 ratio:

$$\text{diCQA}(i,j) + \text{CD} = \text{CD/diCQA}(i), \quad (1)$$

$$\text{diCQA}(i,j) + \text{CD} = \text{CD/diCQA}(j), \quad (2)$$

as well as one complex of 2:1 ratio:

$$\text{diCQA}(i,j) + 2\text{CD} = 2\text{CD/diCQA}(i,j) \quad (3)$$

The spectrophotometric detector in this case is sensitive for all four types of solutes including not involved in complexation solute:

$$\Sigma\text{diCQA}(i,j) = \text{diCQA}(i,j) + \text{CD/diCQA}(i) + \text{CD/diCQA}(j) + 2\text{CD/diCQA}(i,j). \quad (4)$$

In this case total retention will be a sum of retentions of every type of solute that may be calculated as the products of the fraction of these forms in solution, α(i), multiplied by their retention factors:

$$k[\Sigma\text{diCQA}(i,j)] = k_0\cdot\alpha[\text{diCQA}(i,j)] + k_i\cdot\alpha[\text{CD/diCQA}(i)] + k_j\cdot\alpha[\text{CD/diCQA}(j)] + k_{i,j}\cdot\alpha[2\text{CD/diCQA}(i,j)] \quad (5)$$

For the equilibrium (1):

$$K_i = \frac{[\text{CD/diCQA}(i)]}{[\text{diCQA}(i,j)][\text{CD}]}$$

Concentration of the complex in a mobile phase is expressed as:

$$[\text{CD/diCQA}(i)] = K_i[\text{diCQA}(i,j)][\text{CD}]$$

Similarly may be expressed the other concentrations:

$$[\text{CD/diCQA}(j)] = K_j[\text{diCQA}(i,j)][\text{CD}]$$

$$[2\text{CD/diCQA}(i,j)] = K_{i,j}[\text{diCQA}(i,j)][\text{CD}]^2$$

The obtained concentrations may be inserted into equation (4):

$$[\Sigma\text{diCQA}(i,j)] = [\text{diCQA}(i,j)] + K_i[\text{diCQA}(i,j)][\text{CD}] + K_j[\text{diCQA}(i,j)][\text{CD}] + K_{i,j}[\text{diCQA}(i,j)][\text{CD}]^2$$

$$[\Sigma\text{diCQA}(i,j)] = [\text{diCQA}(i,j)](1 + K_i[\text{CD}] + K_j[\text{CD}] + K_{i,j}[\text{CD}]^2) \quad (6)$$

Than molar fractions of all solute forms are:

$$\alpha[\text{CD/diCQA}(i)] = K_i[\text{CD}]/(1+K_i[\text{CD}]+K_j[\text{CD}]+K_{i,j}[\text{CD}]^2)$$

$$\alpha([\text{CD/diCQA}(j)] = K_j[\text{CD}]/(1+K_i[\text{CD}]+K_j[\text{CD}]+K_{i,j}[\text{CD}]^2)$$

$$\alpha[2\text{CD/diCQA}(i,j)) = K_{i,j}[\text{CD}]^2/(1 + K_i[\text{CD}] + K_j[\text{CD}] + K_{i,j}[\text{CD}]^2)$$

Thus the equation (5) may be transformed:

$$k(\Sigma\text{diCQA}(i,j)) = (k_0+K_ik_i[\text{CD}]+K_jk_j[\text{CD}]+K_{i,j}k_{i,j}[\text{CD}]^2)/(1+K_i[\text{CD}]+K_j[\text{CD}]+K_{i,j}[\text{CD}]^2) \quad (7)$$

The equation may be rearranged as follows:

$$\frac{k_0 + k_iK_i[\text{CD}] + k_jK_j[\text{CD}] + k_{i,j}K_{i,j}[\text{CD}]^2}{k(\Sigma\text{diCQA})} = 1 + K_i[\text{CD}] + K_J[\text{CD}] + K_{i,j}[\text{CD}]^2 \quad (8)$$

Quantitative calculation of six unknown constants is complex but the constants may be readily estimated by simplifying the equation (8) by assumption of a small influence of retention of all types of complexes:

$$F(i,j) = \frac{k_0}{k(\Sigma\text{diCQA})} \approx 1 + K_i[\text{CD}] + K_J[\text{CD}] + K_{i,j}[\text{CD}]^2. \quad (9)$$

The plot according to this equation for mobile phase containing 12 vol.% of acetonitrile is presented in the Fig. 3.

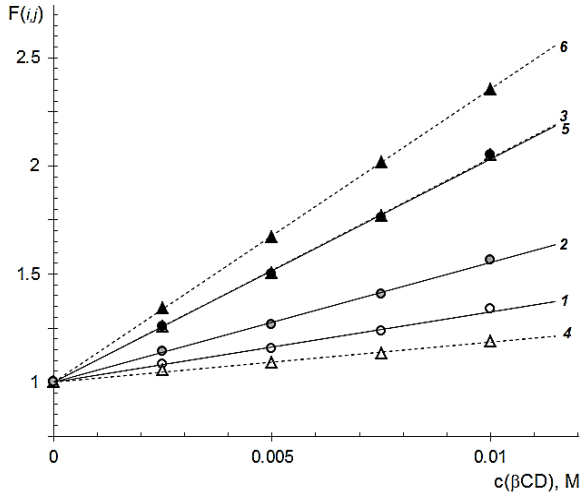

Fig. 3. The dependence of solute retention function according to eq. (9) upon molar concentration of β-cyclodextrin in a mobile phase containing 0.25 vol.% of ortho-phosphoric acid and 12. % of acetonitrile in water. Substances numbering as in Fig. 1

Рис. 3. Зависимость функции удержания растворенного вещества в соответствии с уравнением. (9) при молярной концентрации β-циклодекстрина в подвижной фазе, содержащей 0,25 об.% ортофосфорной кислоты и 12% ацетонитрила в воде. Нумерация веществ, как показано на рис. 1

A special calculations the take into account formation of 1:1 complexes proved that proposed simplification is reasonably enough. Meanwhile a slope for 4,5diCQA is the greatest as a consequence of greatest sum of K_i and K_j. The comparison of the constant value for *i*,*j*diCQA with sum of that for *i*CQA and *j*CQA is quite informative and may indicate sterically restriction for complex formation. Constant of inclusion complex value for 4,5diCQA (135 $mol^{-1}\cdot l$) is only slightly smaller than the sum of constant values for 4CQA (55 $mol^{-1}\cdot l$) and that for 5CQA (104 $mol^{-1}\cdot l$) indicating only small sterically restrictions for entrance of caffeic acids into the cavity of cylodextrin. But for 3,4diCQA (19 $mol^{-1}\cdot l$) the restriction is much more pronounced since this value is less than not only the sum of constant values for 4CQA (55 $mol^{-1}\cdot l$) and that for 3CQA (33 $mol^{-1}\cdot l$) but even less than each of the values for monocaffeoylquinic acids.

The explanation of the results may be roved by consideration of some conformations of 3,4diCQA and 4,5diCQA, that were obtained by geometry optimization by AM1 method in HyperChem™ 8.0.8 program as well as the optimized structure of the inclusion complex of 4CQA in a cavity of β-cyclodextrin, Fig. 4.

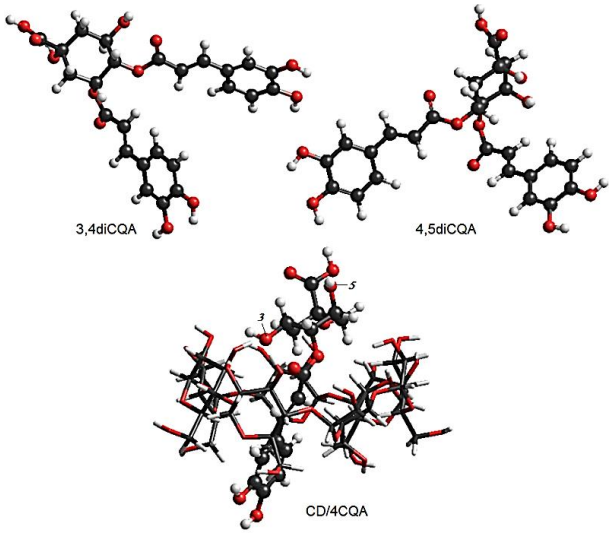

Fig. 4. Geometry optimized conformations of 3,4diCQA, 4,5diCQA and of inclusion complex of 4CQA into β-cyclodextrine cavity

Рис. 4. Оптимизированные по геометрии конформации 3,4diCQA, 4,5diCQA и комплекса включения 4CQA в β-циклодекстриновую полость

Comparing the conformation of 3,4diCQA and the structure of CD/4CQA restrictions for insertion of caffeoyl substituent in position 4 into β-cyclodextrin cavity is sterically hindered by the substituent in position 3 and *vice versa*. Thus the complex formation constant for the isomer is the lowest. Meanwhile there may occur only some restrictions in the case of 4,5diCQA with a greatest constant of complex 1:1 formations while the sterically restriction is obvious for formation of inclusion of the resulted complex into a cavity of a second β-cyclodextrin molecule because of large size of the first β-cyclodetxtrin molecule. This explains the absence of inclusion complexes of β-cyclodetxtrin with diCQAs in ratio 2:1, found by analysis of plots in Fig. 3.

CONCLUSSION

The investigation of chromatographic behavior of chlorogenic acids in reversed-phase HPLC with addition of β-cyclodextrin into a mobile phase proved to alter the separation selectivity of monocaffeoylquinic as well as dicafeoylquinic acids. The alteration is the consequence of the dependence of values of "host-quest" complex formation for different isomers. Qualitatively the set of 1:1 complex formations values of dicaffeoylquinic acids depends the summs of the values of complex formation for monocaffeoylquinic acids with corresponding positions of caffeic acid substituents in quinic acid. Because of high sterically restrictions value of the complex constant for 3,4diCQA becomes the lowest, while that for 4,5diCQA is the greatest as well as the formation of 2:1 complexes is sterically prohibited for all these diCQAs.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

The authors declare the absence a conflict of interest warranting disclosure in this article.

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