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Modified aqueous mobile phases: A way to improve retention behavior of active pharmaceutical compounds and their impurities in liquid chromatography

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ABSTRACT

Most commonly used analytical technique for determination of active pharmaceutical ingredients and their impurities in quality control throughout all phases of drug research, development and manufacture is definitely reversed-phase high performance liquid chromatography (RP-HPLC). However, pharmaceutical industry professionals are often faced with various challenges in RP mode, which cannot be resolved with common variations in the composition of the mobile phase. These challenges often occur when analyzing compounds that contain basic ionizable groups, possess large differences in polarities and require consumption of high amounts of toxic organic solvents. Among available strategies for addressing the aforementioned issues, the most convenient one includes RP-HPLC mobile phase modifications by an addition of the proper chemical compounds. In that respect, RP-HPLC method can be easily adapted to the needs of the analysis without time-consuming and expensive equipment procurement. In this review the chaotropic chromatography, micellar liquid chromatography, and cyclodextrin modified RP-HPLC systems are presented and discussed in details. Special attention is devoted to the theoretical background, the possibility of retention modeling and applications in various fields of pharmacy, as well as their prospective in further research.

1. Introduction

Nowadays reversed-phase high-performance liquid chromatography (RP–HPLC) is the most versatile and widespread analytical technique that plays a vital role in quality control throughout all phases of drug research, development and manufacture. Thirty years ago, it was estimated that 80% - 90% of all analytical separations were performed by using RP chromatographic mode. To a great extent, the analytes retention and selectivity could be modified with variations in the mobile phase composition. In the past decades certain things changed including the development of large number of the stationary phases with modified chemistry and/or geometry. However, the mobile phase remained the major force that significantly influences the analytes' retention. The modifications of the mobile phase composition, in terms of pH, type and amount of organic modifier, buffer type and concentration, provide the RP-HPLC methods with the ability to modulate the analytes' retention and separation [1, 2].

However, certain drawbacks of RP-HPLC methods were recognized over the years. They were mainly related to the impossibility to adjust the analytes' retention on the basis of the above stated chromatographic parameters, exclusively. Accordingly, the aim of this paper was to describe some of the modifications of the RP-HPLC method, in the first line mobile phase modifications (Figure 1), which made it possible to overcome the common issues occurring with chromatographic methods. Mobile phase modifications are extremely convenient, because the chromatographic method can be quickly adapted to the needs of the analysis without time-consuming and expensive equipment procurement. These kinds of modifications are simple and obtained with the addition of the appropriate chemical substances to the mobile phase. In this paper, chaotropic chromatography, micellar liquid chromatography (MLC) and cyclodextrin-modified RP-HPLC systems will be elucidated in detail.

Chaotropic chromatography is related to the analysis of the base active pharmaceutical ingredients (APIs) and their impurities. The analysis of drugs that contain basic ionizable groups by RP-HPLC is generally influenced by numerous issues mainly related to their protonation within the pH range suitable for the chromatographic bed of silica-based stationary phases. Namely, majority of basic drugs comprise ionizable groups with pKa values above 6 and most commonly around 9 [1]. For appropriate retention in RP-HPLC an adequate solute's form has to be in-

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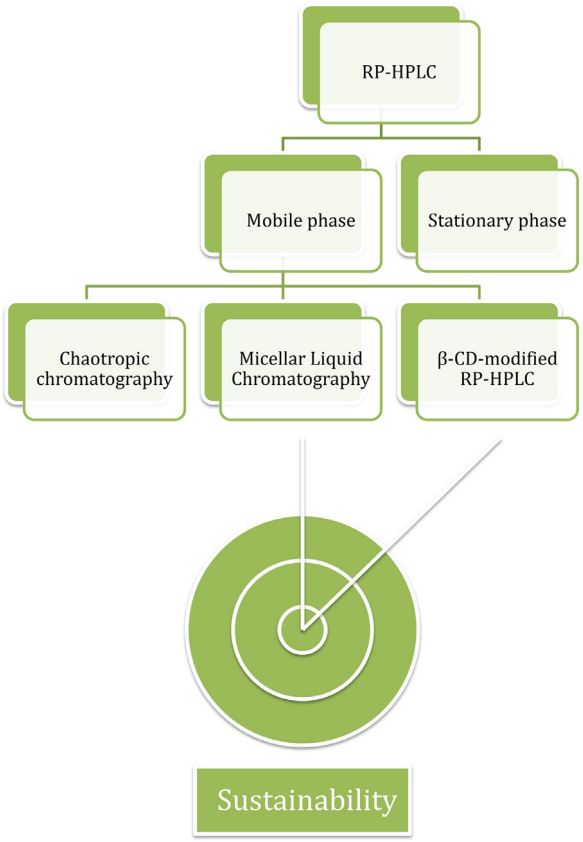

Fig. 1. Schematic representation of different mobile phase modifications in RP-HPLC.

duced by complete suppression of ionization. Therefore, for the analysis of basic solutes mobile phase pH requires adjusting to approximately 8 – 11, which lies outside the acceptable operating range of reversed-phase silica-based stationary phases. The presented issues could be effectively addressed by chaotropic chromatography [3].

When analyzing hydrophilic drugs, the analysts are faced with early eluting peaks in the RP-HPLC. In order to prolong the elution and enable proper determination, MLC technique stood out as a proper solution. On the other side, the micelles surround the hydrophobic drugs and reduce their retention in the RP-HPLC systems. Accordingly, this property is often utilized when separating the analytes with huge diversity in polarities and charges. This is a very common situation when developing stability-indicating methods or analyzing multicomponent drugs. Though the gradient elution mode could be applied in this situation, these kinds of methods are characterized with relatively poor reproducibility and time-consuming analysis. Since MLC methods are performed with no or little amount of organic modifier, with surfactants that are biodegradable, less toxic and less flammable compared to conventional RP-LC hydro-organic mixtures, these methods are also associated with ecological acceptability, which is one of the major concerns nowadays [4, 5].

Recently growing interest is based on the use of cyclodextrins (CDs) as mobile phase additives taking into account their cost-to-benefit ratio, semi-natural origin and eco-friendly character. CDs generate inclusion complexes with versatile organic analytes increasing their water solubility. In this way, the analytes are less retained in the RP-HPLC system, the chromatographic run is shorter, which causes lower consumption of the toxic organic modifiers, but without loss in the resolution or efficiency of separation [6]. These systems have great ecological potential, but have not been still investigated in depth, therefore their so far known power of greening and associated applications are described.

2. Chaotropic chromatography

2.1. Theoretical background

Ion-interaction chromatography (IIC) is reliable, well established approach that must be considered if ionization suppression is not a feasible option in obtaining acceptable retention behavior. This chromatographic mode is intermediate between reversed-phase and ion-exchange chromatography that implies employment of characteristic eluent containing ion-interaction agent (IIA). These agents are mainly amphiphilic or lipophilic in nature with the tendency to accumulate onto the hydrophobic stationary phase surface leading to the formation of a pseudo-exchange surface. Consequently, chromatographic behavior is modulated by electrostatic interactions between charged solutes and the oppositely charges IIAs both on the pseudo ion-exchange surface and in the mobile phase leading to adequate retention, peak shape and separation efficiency [3].

For decades amphiphilic additives that contain a charged group attached to a long alkyl chain are used as IIAs in chromatography. Their application usually results in permanent modification of reversed-phase stationary phase which acquires ion-exchange character that limits its usability and lifetime. Conversely, many small inorganic and organic liophilic ions exhibit the same beneficial effects on the retention of charged solutes in RP-HPLC systems but their effect on the column properties is reversible. These ions have the ability to perturb the ordered structure of water and introduce chaos in the structure of the ionic solution and as a consequence they are named chaotropic agents while IIC employing these IIAs is simply referred as chotropic chromatorgraphy.

IIC chromatographic system is quite complex and commonly described through a series of equilibria and the corresponding stoichiometric equilibrium constants [3, 7]:

(1) adsorption of the IIA (H) to surface ligand site (L) and formation of a charged surface site (LH)

$$L + H \overset{K_{LH}}{\rightarrow} LH \tag{1}$$

(2) adsorption of the analyte (E) to the stationary phase site L

$$L + E \overset{K_{LE}}{\rightarrow} LE \tag{2}$$

(3) ion pairing in the stationary phase (LEH) for the oppositely charged analyte and IIA

$$E + H + L \overset{K_{LEH}}{\rightarrow} LEH \tag{3}$$

$$E + LH \overset{K_{LEH}/K_{LH}}{\rightarrow} LEH \tag{4}$$

$$EH + L \overset{K_{LEH}/K_{EH}}{\rightarrow} LEH \tag{5}$$

(4) ion pairing in the mobile phase (EH) for the oppositely charged analyte and IIA

$$E + H \overset{K_{EH}}{\rightarrow} EH \tag{6}$$

(5) displacement of H by E

$$E + LH \overset{K_{LE}/K_{LH}}{\rightarrow} LE + H \tag{7}$$

Obviously, specific ion effects occur both in bulk solution and at the interfaces so the understanding of the effectiveness of chaotropic agents as IIAs requires careful thereof consideration. These specific effects were firstly described by Franz Hofmeister who ranked ions in so called Hofmeister series differentiating them from “structure makers” or kosmotrope ions to “structure breakers” or chaotrope ions [8]. The series can be written as: $CO_3^{2-} < SO_4^{2-} < S_2O_3^{2-} < H_2PO_4^- < OH^- < F^- < HCOO^- < CH_3COO^- < Cl^- < Br^- < NO^{3-} < I^- < ClO_4^- < SCN^-$ where the thiocyanate ion would be the most chaotropic, and carbonate the

least chaotropic ion in the series. Anions that are regularly used as mobile phase additives in chaotropic chromatography are $CF_3COO^- < BF_4^- < ClO_4^- < PF_6^-$ in the rank of increasing chaotropicity [9]. The ability of chaotropic ions to impair solvation shell around analyte is an important in depicting the effectiveness of these agents in ion-pair formation with oppositely charged organic solutes. Furthermore, chaotropes are also adsorbophilic species, the rank of an increasing chaotropicity correspond with their tendency to accumulate onto the reversed-phase stationary phase surface and can be quantified through adsorption isotherms [10, 11]. The effectiveness of chaotropic agents in extending the retention of the oppositely charged solutes is associated with its adsorbophility. Assuming that chaotropic anion is much more adsorbophilic then its counterion, the surface of the stationary phase is reversible charged due to formation of the adsorbed layer of the chaotropic agent. Consequently, electric double layer is formed since oppositely charged ions from the eluent are then attracted to the charged surface. The solute is predominantly adsorbed onto the surface due to the developed electrostatic potential [12, 13].

Retention mechanisms in ion-interaction chromatography were debated extensively in the literature with several contradictory perspectives on key factors that govern retention in these systems [14–16]. Probably the most comprehensive theoretical model up to this point has been proposed by Cecchi et al. [17]. The authors refer to this model as an extended thermodynamic approach since it encompasses the most relevant equilibria from the stoichiometric description of the IIC system and introduces thermodynamic equilibrium constants. Although the model was originally proposed for systems with classical amphiphilic IIAs, it was successfully applied for describing retention behavior in chaotropic chromatography on several occasions, as the only distinction is the comparatively low adsorbophilicity of chaotropic agents used in the latter systems [9, 18-21]. The final form of the model is presented by Eq. (8):

$$k = \frac{c_1\left\{a[H]^b f + \left[\left(a[H]^b f\right)^2 + 1\right]^{0.5}\right\}^{\pm 2|z_E|} + c_2[H]}{\left(1 + c_3[H]\right)\left\{1 + c_4[H]\left\{a[H]^b f + \left[\left(a[H]^b f\right)^2 + 1\right]^{0.5}\right\}^{(-2|z_H|)}\right\}} \quad (8)$$

Parameter c_1 equals k_0, the retention factor of the analyte without chaotropic additive in the eluent, it can be experimentally obtained and generally is not considered adjustable. The other three parameters c_2, c_3 and c_4 are related to the thermodynamic equilibrium constants for the ion-pair formation in the stationary phase, for the ion-pair formation in the eluent and for the adsorption of the ion-interaction reagent onto the stationary phase, respectively. The last term (c_4) can be omitted from the fitting procedure due to relatively low adsorbophilicity of common chaotropic salts.

2.1.1. Factors governing the retention behavior in chaotropic chromatography

Key empirical findings related to how retention phenomena in chaotropic chromatography are affected by mobile phase composition, type of the chaotropic agent and the chemistry of stationary phase are summarized in Vemić et al. [7]. The factors perceived to influence the retention behavior of protonated basic solutes the most, hence extensively studied, are the type of the chaotropic salt and it concentration in the mobile phase. In brief:

- increasing chaotropicity of IIA promotes solutes' retention,
- graphical representation of retention factor vs. chaotrope concentration follows increasing trend up to a certain concentration of chaotrope IIA when plateau is reached and
- solute's hydrophobicity is limiting factor in so called "chaotrope sensitivity" i.e. highly hydrophobic solutes typically experience pronounced increase in retention with the addition of chaotropic agent.

These findings were mainly rationalized by the formation of stable ion pairs between oppositely charged chotrope ion and analyte once its solvation layer is disrupted with the increased chaotrope concentration [22, 23]. However, it was experimentally verified that the differences in adsorbofilicity of various chaotropic anions play the crucial role in modulation of oppositely charged solutes retention. Increasing chaotropicity of IIA favors larger surface excess of the chaotrope anions on the stationary phase, consequently larger surface potential is developed leading to longer retention of positively charged solutes [19]. With the aid of extended thermodynamic approach and ropinirole as example Vemić et al. confirmed that analyte's retention is a combined result of changes in ion pairing in the mobile phase and magnitude of the surface potential [18]. Namely, increasing chaotrope concentration is contributing both surface potential rise that promote a linear increase in retention and ion pairing in the mobile phase that results in linear decline in retention. Therefore, accurate description of the experimentally observed retention behavior can be obtained only when both effects of increasing chaotrope concentration are considered simultaneously.

There is a complex interplay between chemistry of stationary phase, organic modifier content in the mobile phase and the adsorption of various chaotropic anions onto the stationary phase surface. In chaotropic chromatography type of the organic modifier and its mobile phase fraction have convoluted effects on the overall solute's retention behavior. It is well established that methanol forms monolayers on hydrophobic stationary phases, while ACN and THF are capable of forming adsorbed layers more than 10 Å thick [24]. Therefore, commonly employed organic modifiers can affect not only eluent strength, but also the adsorption of the chaotropic agent. Namely, ACN adsorption onto the stationary phase surface strongly benefit adsorption of chaotropes following the rank of increasing chaotropicity. On the other hand, such enhancement is very moderate in the case of methanol. However, the increase in ACN content in the mobile phase above a certain value leads to opposite effects since the stationary phase is approaching saturation and elution capacity of the mobile phase is increased leading to the decline of retention factor [10, 11]. Kazakevich et al. verified that increasing stationary phase hydrophobicity (perfluorophenyl to alkylphenyl, n-alkyl to graphite) assist the adsorption of both ACN and the chaotropic agent promoting the development of larger surface excess especially when PF_6^- was considered [10, 11]. Vemić et al. analyzed data obtained for basic pramipexole and its 5 impurities (4 of basic character and 1 neutral) by modeling them within the framework of extended thermodynamic approach. Results were used to rationalize the effects of varying stationary phase chemistry, chaotropic salt type and its concentration in the mobile phase. Fitted coefficients c_2 and c_3 have a clear physical meaning thus c_2/c_3 ratio was used to interpret the way hydrophobicity of the column affects the retention phenomenon. Obviously, increasing stationary phase hydrophobicity favors ion-pair formation in the stationary phase while the relative magnitude of this effect was found to be approximately proportional to the chaotropicity of the anion in question [19].

For many years the effect of mobile phase pH on retention behavior in IIC was evaluated from the point of its effect on the solute ionization state - lowering pH favors the protonated microspecies, enhance interaction of the oppositely charged ions resulting in the longer retention times [25]. It was first demonstrated by Čolović et al. that mobile phase pH has more profound influence on retention in chaotropic chromatography [20]. Retention behavior of a set of diverse basic drugs was investigated in the systems modified with $NaPF_6$ and the pH of the aqueous part of the mobile phase adjusted from 2 to 4 to assure full protonation of considered analytes. The increase in pH resulted in prolonged retention of fully protonated analytes which was rationalized by further investigation of pH effect on the adsorption of the chaotropic agent onto the stationary phase. The surface excess of PF_6^- is consistently larger at higher pH values within the investigated range and this could not be explained by the chemical nature of anion itself. In line with the previously discussed findings by Kazakevich et al. [10, 11] we hypothesized that the altered ACN adsorption could justify the altered

adsorption of chaotropic agent. It was experimentally confirmed that increasing pH from 2 to 4 significantly enhanced ACN surface excess especially in range from 30% to 40% of ACN. The potential explanation for pH modulated adsorption of ACN is that residual silanol groups are ionized at higher pH values, the ordered nature of silanol-bonded alkyl chains is affected and high-affinity sites for ACN binding are created [24, 26]. Nevertheless, additional experimental studies are needed to extend and further test the theory we have conferred.

All previously presented findings originate from an experimental set whose ionic strength (*I*) was varied with the concentration of the chaotrope and the additives used to adjust pH of the mobile phases. It is well known fact that the increase in the surface potential can be influenced by ionic strength [17] hence we investigated whether the observed retention behavior of completely protonated solutes and chaotropic ion adsorption were caused by a mobile phase pH variance or ionic strength effects. The pH-dependent retention behavior of fully protonated basic solutes in chaotropic chromatography was distinguished from ionic strength effects with the aid of extended thermodynamic approach [21]. The significance of ion-pairing in the stationary phase of systems with varying *I* was confirmed and quantified via estimation of c_2 fitting parameter. On the other hand, in the experimental set with a constant *I*, decrease of retention was observed upon addition of NaCl due to the counterion effects on chaotropic anion adsorption and development of surface potentials significantly subsided and almost constant in all investigated systems. Furthermore, competition between excess Na^+ and positively charged analyte ions for the adsorbed chaotropic ions abated electrostatic interactions and ion-pairing in the stationary phase. It is worth noting that new research opportunities have come about since supplementary investigation is needed on how to apprehend the impact and outcomes of the effect of the type and the nature of counter ion of both the chaotropic agent and the ionic strength modifier on basic solute retention behavior in chaotropic chromatography [21].

2.2. Modeling the relationship between analyte's structure and its retention in chaotropic chromatography

Extended thermodynamic approach treats retention data in a way that provides information for accurate and exhaustive insight into specific processes underlying retention behavior of individual analyte in IIC. Conversely, quantitative structure-retention relationship (QSRR) modeling is based on the theoretical framework that provides a basis for relating analytes' physicochemical properties to their chromatographic behavior in a quantitative manner [27–29]. QSRR modeling has been extensively used in conventional RP-HPLC, while for IIC a very small number of studies exist probably due to inherent complexity of the system. Nevertheless, foundation has been laid over the past few years with so called "mixed modeling" in chaotropic chromatography as an encouragement for further research in the field [20]. "Mixed modeling" proved to be more practical and general approach which involves incorporating both mobile phase and structural descriptors into the model as independent variables.

Several years ago the study of the effect of solutes' structure on their retention behavior in chaotropic chromatography commenced with the pramipexole and its impurities as pharmaceutically relevant example [19]. The influence of molecular structure on the retention behavior was rationalized by correlating the values of the calculated molecular descriptors with the fitting parameters of the extended thermodynamic model. In brief, the results of this analysis suggested that the charge distribution in solutes' electronic structure and its complementarity to the electric double layer formed on the surface of the stationary phase can be useful for understanding the differences in retention of structurally related analytes. In the next study more generally applicable QSRR model was established since the modeling involved retention data obtained for 34 structurally diverse analytes in 36 chromatographic systems [20]. "Mixed modeling" approach and support vector regression were used to correlate chromatographic parameters and values of analytes' structural descriptors to retention data. The final model included 4 molecular descriptors and 3 mobile phase descriptors (%ACN, pH and NaPF6 concentration both related to the aqueous phase). The four molecular descriptors included in the developed model were: ETA_Eta_B_RC (branching index EtaB, with ring correction, relative to molecular size), XlogP (calculated octanol/water partition coefficient), TDB9p (3D topological distance based autocorrelation – lag 9/weighted by polarizabilities), and RDF45p (radial distribution function – 045/weighted by relative polarizabilities). Although molecular descriptors ETA_EtaP_B_RC and XlogP describe factors affecting retention in any RP-HPLC system, TDB9p and RDF45p are molecular descriptors which account for spatial arrangement of polarizable atoms and they can clearly relate to retention phenomenon on the stationary phase surface where the electrostatic potential developed. As a key factor influencing solutes' retention behavior, complementarity of analytes' structure with that of the electric double layer was identified.

Although extended thermodynamic modeling lacks predictive capabilities and does not account for solute's chemical structure effect on retention phenomenon, its fitting parameters provide sound basis for development of empirical model that would take into account both chemical structure of analyte and contribution of various chromatographic parameters to the specific processes. Therefore, we developed a readily interpretable empirical retention model tailored to describe the retention of charged species in the presence of oppositely charged chaotropic ions [21]. The final form of the model simultaneously takes into account analyte molecular structures and the most relevant chromatographic factors while its coefficients have clear physical meaning:

$$k = k_0 + e * \mu * ln|\psi| * LaI + s * L2p^2 * [H] - m * [H] \quad (15)$$

where k_0 is the retention factor in absence of a chaotropic additive and *e, s*, and *m* are fitting system-specific parameters accounting for the contribution of the interaction with the electric double layer to analyte retention, ion pairing in the stationary phase and ion pairing in the mobile phase, respectively. The other variables are analytes' structural features governing specific processes underlying separation in chaotropic chromatography: μ - the magnitude of the analyte's dipole moment, Ψ - the surface potential, *LaI* - the lipoaffinity index, *L2p* - 3D molecular descriptor that simultaneously consider both the size and shape of a molecule and the spatial distribution of atoms, weighted by their atomic polarizabilities and [*H*] - the mobile phase concentration of the chaotropic salt. Single optimized 3D molecular structure, chosen as the conformer with the largest dipole moment from a representative ensemble, was used for the calculation of all the molecular descriptors.

Model was applied to collected experimental data and its good predictive capabilities were verified. In the computational models, statistically insignificant ($p>0.01$) values of *m* indicated the ion-pairing processes in the mobile phase to be irrelevant to the retention of analytes in all studied systems. In the chromatographic systems with a constant *I*, the negligible pH-dependent variance of the *e* and s parameters was observed while in the chromatographic systems with varying *I*, ion pairing in the stationary phase was not affected with the changes in the mobile phase pH values and the values of the parameter *e* increase with pH. These observations once more verified the relevance of solutes interactions with the double layer in describing the observed thereof retention behavior in the studied systems.

2.3. Chaotropic chromatography – application in analysis of APIs and impurity profiling

Scientific documents published in the field of chaotropic chromatography in the period from 2012 to 2021 according to the Web of Science platform accessed on November 2021 count 101 papers. However, those published in the domain of pharmaceutical analyses are limited to only 15. Although the application field is broad, this chromatographic mode is still not extensively used and can be considered pioneering. It is mainly used to overcome the problems of poor retention of small, polar,

Table 1
Summarized applications of chaotropic chromatography (2017 – 2021).

Analytes	Sample	Chromatographic system	Elution mode and column temperature	Ref.
Melamine	Infant formula	Develosil RP-Aqueous C30 column (150 mm × 4.6 mm,5 μm particles), mobile phase consisted of 35 mM sodium hexafluorophosphate (NaPF6) in 0.1% acetic acid (pH 3).	Isocratic elution, 30 °C	[30]
Urocanic acid	Fish	Allure C18 column (150 mm × 4.6 mm, 5 μm particles), binary mixture of (A) water containing KPF6 and phosphoric acid (10 mM each), and (B) CAN	Isocratic elution, 32 °C	[31]
Proteins	Standard mixture	Halo C4 column(2.1 mm × 75 mm, 2.7 μm particles), mobile phase A: 0.1% TFA in H_2O / 1 M sodium perchlorate monohydrate in perchloric acid in H_2O / 1 M guanidine hydrochloride in H_2O and mobile phase B: CH3CN	Gradient elution, 7 different temperatures (20 °C – 80 °C)	[32]
Aripiprazole and impurities	Pharmaceutical drug product	XTerra C8 column (150 × 4,6 mm, 3.5 μm particles), mobile phase: 34% of acetonitrile, 66% of 42.5 mM perchloric acide	Isocratic solution, 35 °C	[33]
Risperidone and its three impurities	Bulk	Acetonitrile content in the mobile phase (20% – 30%), the pH of the aqueous phase (3.00 – 5.00), the content of chaotropic agents in the aqueous phase (10 mM – 100 mM), type of chaotropic agent (NaClO4, CF3COONa), and stationary phase type (Zorbax Eclipse XDB, Zorbax Extend)	Isocratic elution, 30 °C	[34]
Pharmaceutical intermediates and impurities	Bulk	Sub-2 μm C18 stationary phase (2.1 mm × 50 mm, 1.7 μm particles) with a non-conventional chaotropic mobile phase buffer (35 mM potassium hexafluorophosphate in 0.1 phosphoric acid/acetonitrile)	Gradient elution, 40 °C	[36]
Trimetazidine dihydrochloride and two impurities	Bulk	XTerra column (150 mm × 4.6 mm, 3.5 μm particles), 27% acetonitrile in mobile phase, 63% 170 mM perchloric acid in aqueous phase (pH 3.60).	Isocratic elution, 25 °C	[37]
Atorvastatin and lisinopril	Pharmaceutical drug product	LiChrosorb C8 column (125 mm x 4 mm, 5 μm particles), mobile phase composed of potassium dihydrogen phosphate (10 mM), acetonitrile and potassium hexafluorophosphate (55:45:0.4, v/v/v)	Isocratic elution, 42 °C	[38]
Lamotrigine and its impurity A and impurity G	Pharmaceutical drug product	Zorbax Extend C18 column (150 mm × 4.6 mm, 5 µm particles), 23% of acetonitrile in the mobile phase, 77% of aqueous phase containing 140 mM of perchloric acid (pH 2.50)	Isocratic elution, 30 °C	[39]

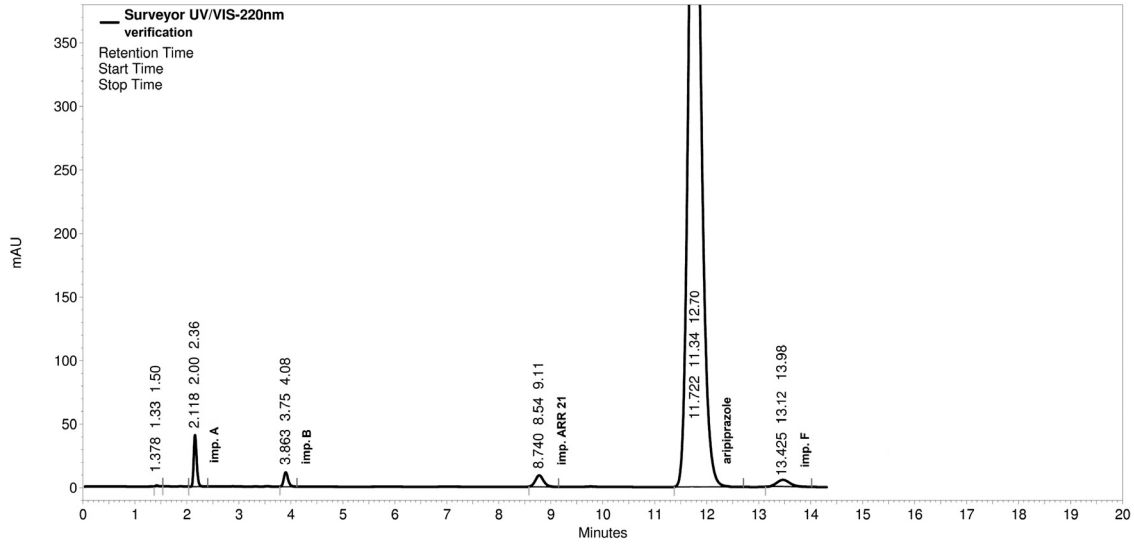

Fig. 2. Chromatogram of sample solution containing 100 μg/mL of aripiprazole spiked with impurities at LOQ obtained under conditions given by the working point (34% of acetonitrile, 66% of 42.5 mM HClO4, 35 °C column temperature and pH of the aqueous phase adjusted at 2.50 with 10 M sodium hydroxide, UV detection at 220 nm, flow rate 1 mL min^{-1}) [33].

basic solutes in pharmaceutical and food domain. Table 1 summarizes the most common applications of chaotropic chromatography in five recent years [30–39].

Analytical scientists are commonly facing the issues of chromatographic separation, especially when dealing with heterogeneous mixtures, differing in polarity and/or acidic-basic characteristics. Aripiprazole and its impurities represent the mixture likewise the above mentioned, therefore chromatographic chromatography was successfully applied for its determination in tablets [33]. Figure 2 illustrates good separation efficiency as well as peak shape of all peaks when using chaotropic chromatography [33]. Moreover, chaotropic method was developed for separation of lamotrigine and its impurities in tablets [39]. Their separation with regular RP-HPLC was precluded by numerous issues mainly related to protonation of solutes. Chaotropic chromatography method for accurate determination of lamotrigine and its two impurities in tablets was developed using experimental design approach, which enabled efficient determination of optimal separation conditions [39]. Furthermore, the addition of chaotropic agent to the mobile phase was shown to be beneficial in isocratic elution method intended for the determination of pramipexole and its impurities in tablets [40], as well

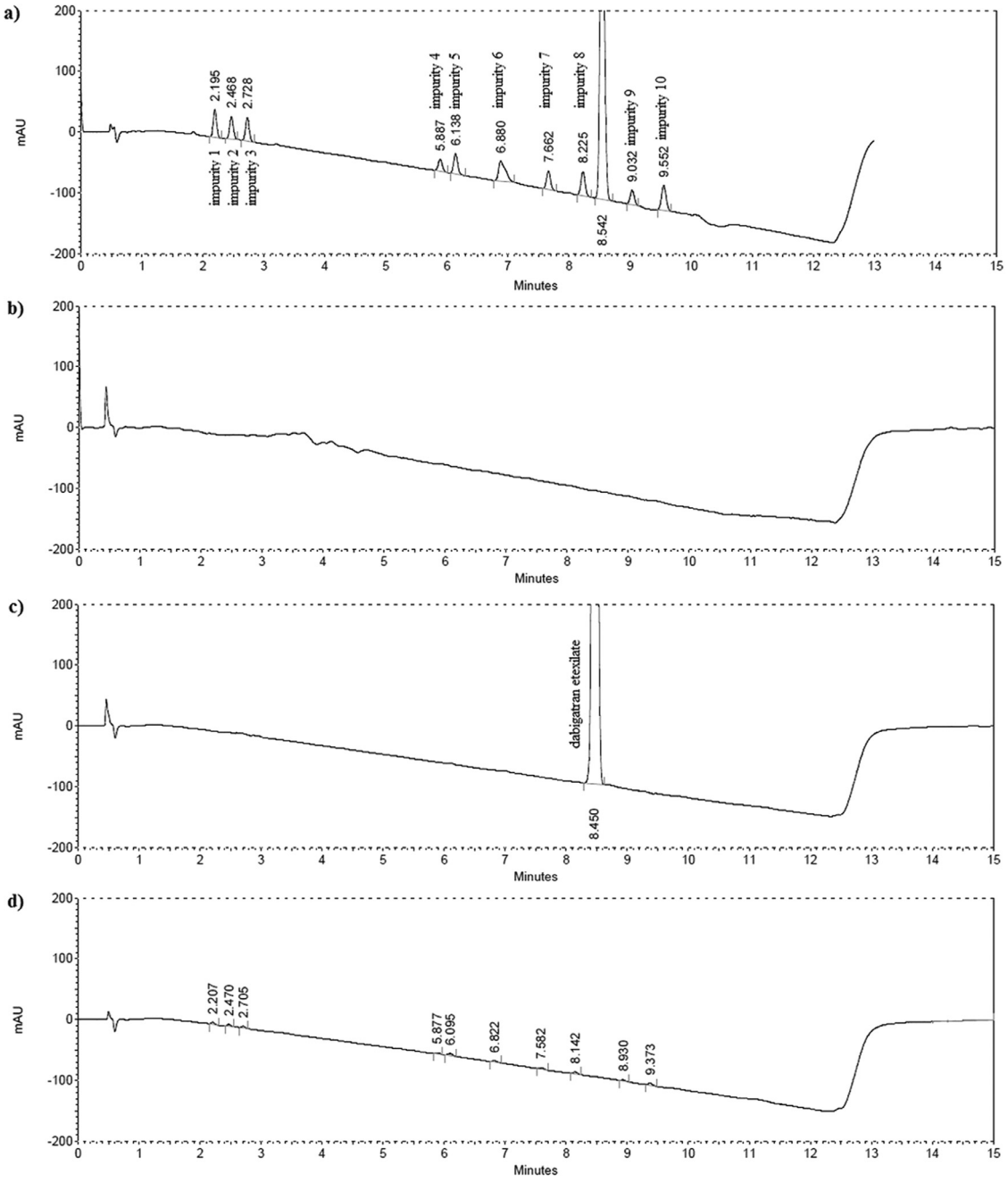

Fig. 3. Chromatograms obtained under the chromatographic conditions given by the working point: 22% acetonitrile at the start of gradient program, 55.5% acetonitrile at the end of gradient program, gradient time 11.5 min, the aqueous phase 150 mM TFA, pH 3.5 adjusted with sodium hydroxide, UV detection at 242 nm, flow rate 3 mL/min, column temperature 45 °C: (a) laboratory mixture, (b) placebo, (c) sample solution containing 1 mg mL^{-1} dabigatran etexilate, and (d) standard solution containing all impurities at LOQ concentration level [41].

as in gradient elution method for the analysis of dabigatran etexilate mesilate and its ten impurities in capsules (Figure 3) [41]. Both preceding methods were developed following analytical quality-by-design principles (AQbD).

The addition of chaotropic reagent to the mobile phase significantly improves the main indicators of peak shape, asymmetry factor and column efficiency in the separation of amlodipine and its impurity A [42]. Additionally, risperidone and its three impurities were used as basic solutes in protonated form to investigated the performance of bonded stationary phases in chaotropic chromatography [34]. Addition of the so called column friendly mobile phase additives – chaotropic agents seems as a reasonable solution to overcome the problems of either unsatisfactory retention of unacceptable peak shape [25, 43], since it outreached the efforts of column manufacturers to develop the silica support providing an adequate performance for basic solutes. Čolović et al. concluded that stationary phase extra densely bonded and double end-capped with trimethylsilyl group enable improved separation performance for basic solutes in chaotropic chromatography [34]. Unsatisfactory retention behavior and/or deteriorated peak shape in regular RP-HPLC led to the development of chaotropic chromatography method for separation of trimetazidine dihydrochloride and its two impurities [37]. Chaotropic chromatography also finds its purpose in food research, when dealing with small size molecules with strong polar nature, which is leading to poor retention [30, 31]. Chaotropic agents are also used in method

development enabling chromatographic resolution of multicomponent reaction mixtures of closely related compounds in the context of process chemistry optimization [36].

3. Micellar liquid chromatography

3.1. Theoretical background

MLC is one of the most useful LC modes that utilize a mobile phase with a surfactant above the Critical Micellar Concentrations (CMC). In the MLC environment, the hydrophobic stationary phase is coated with surfactant monomers, while the mobile phase is characterized by the presence of surfactant in a spontaneously aggregated, micellized form. The plethora of consequently provided interactions between system constituents and analytes offers unique selectivity and modulated retention with regard to analog RP-LC [44–46].

Contemporary application of MLC technique is especially fueled by: 1) Eco-friendly micellar mobile phases that are rich in water and require the addition of only a small amount of organic modifier to reduce long retention of apolar compounds, i.e. enhance peak asymmetry. Micellar eluents, therefore, are biodegradable, less toxic and less flammable compared to conventional RP-LC hydro-organic mixtures; 2) The possibility to separate analytes that differ greatly in polarity and ionizability within single isocratic run; 3) The great ability of micelles to solubilize analytes, which allows direct injection of physiological fluids into the column, that is, skipping the tedious step of sample pretreatment. At the same time, adsorption of a nearly constant quantity of surfactant molecules on the stationary phase leads to stable column properties and highly reproducible retention, while the presence of micelles in the mobile phase reduces evaporation of organic solvent making them stable over time [5].

Unfortunately, MLC suffers from weak elution strength of micellar solvents (especially when used in conjunction with RP-LC columns of typical pore size) and questionable efficiency, which dramatically impair its widespread use. Reduced efficiency, due to poor wetting of the stationary phase and slow analyte mass-transfer, can be addressed by adding a small amount of organic modifiers to the mobile phase (usually, short chain alcohols) and raising the working temperature [47]. Dorsey et al. [48] were among the first to introduce the mentioned practice in MLC, reporting that the addition of 1-propranolol to the mobile phase and setting the column temperature to 40 °C made the behavior in micellar system close to classical RP-LC system regarding the peak shape. Since then, effect of temperature increase on the column efficiency has been examined by several research groups [47, 49, 50]. In most of these studies, micellar mobile phases contained the anionic surfactant SDS. More recently, Baeza-Baeza et al. [51] analyzed flavonoids under Brij-35-mediated MLC conditions. They found that increasing the temperature up to 80 °C enhanced the efficiency to the extent that it was similar to acetonitrile-water RP-LC mode. Along with the described strategy, the use of hybrid mobile phases has become common practice to mitigate the poor efficiency of MLC chromatographic technique. This is due to the ability of the organic solvent to reduce the viscosity and thickness of the adsorbed surfactant on the stationary phase. As additional benefit, organic solvent increases the elution power of the MLC eluent.

In recent years researchers started using mixed micellar mobile phase to eliminate the need of an organic modifier, cutting even more the environmental costs of LC procedures. For this purpose, more polar nonionic surfactant Brij-35 is favorably used in conjunction with SDS due to appealing ability to modulate the polarity of the stationary phase without impacting the net charge [52].

3.1.1. Surface active agents

Surface Active Agents, or contracted, surfactants are amphiphilic compounds that contain both a polar (hydrophilic) head group and a non-polar (hydrophobic) tail (e.g. hydrocarbon chain and bile salts). Based on the nature of the hydrophilic group, surfactants are classified as: ionic (anionic and cationic), nonionic and amphoteric (zwitterionic) surfactants. At low concentrations, the surfactant molecules reside at the surface, i.e., the interface of the two-phase system and alternate to some extent the corresponding free energies. Saturation of surface/interface with surfactant molecule at the higher concentrations triggers their grouping into dynamic aggregates denoted as micelles. The concentration at which the self-organizing phenomenon occurs represents the CMC. The spherical-shaped, normal-phase micelles have heads oriented toward water, whereas the tails stay in the core.

From the aspect of interaction, micelles are formed at a delicate moment when steric and electrostatic repulsive interactions between the head groups are balanced by forces that promote micellization (hydrophobic interactions between tails). Nonionic surfactants are free of electrostatic forces, causing micelles to be formed at lower CMCs than ionic ones. Besides CMC, the values of Krafft point (minimum temperature at which micelles can be formed), aggregation number, shape and size of micelles vary between surfactants. The features of the most commonly utilized surfactants in MLC, such as the anionic sodium dodecylsulfate (SDS), the cationic cetyltrimethylammonium bromide (CTAB) and the non-ionic Brij-35 are given inTable 2 [53].

In MLC, surfactants should be applied in a concentration greater than CMC. However, a concentration higher than 200 mM is not recommended due to the high viscosity of such solutions. Commonly applied concentrations are: 10 – 50 mM for Brij-35, 40 – 100 mM for CTAB and 50 – 150 mM for SDS. For anion and cationic surfactants, the chromatographic analysis should be performed above the Krafft point to prevent surfactant precipitation. The values of Krafft point are impacted by the salt presence [5].

3.1.2. MLC system components

Every MLC system contains a non-polar stationary phase coated with surfactant molecules and an aqueous mobile phase (usually) modified with a certain amount of organic solvent. In addition to a mixture of water and an organic solvent, colloidal micellar aggregates are present, as well as individual molecules of the selected surfactant at a concentration approximately equal to CMC.

3.1.2.1. The stationary phase. Analyzes in MLC are typically performed using C18 (octadecylsiloxane) stationary phases. Under MLC conditions, the stationary phase is coated with adsorbed monomers, adopting, in fact, the structure of open micelles. As a consequence, the properties of the packing material (such as structure, pore volume and polarity) alter, which dramatically affects the chromatographic behavior of tested compounds. It is important to note that adsorbed nonionic surfactants change only the polarity of the stationary phase, while with ionic surfactants a certain amount of charge appears on the surface of the modified column. In some cases, a reduction in silanol activity is observed.

The amount of adsorbed surfactant in the stationary phase is directly proportional to the surfactant concentration as shown in [54]. In the case of C18 stationary phases, the adsorption of the surfactant monomers reaches the saturation level (plateau) at (or before) CMC, producing a column of stable characteristics. However, for some surfactants, the adsorption of monomers continues at concentrations above CMC. According to Borgerding et al. [55] this was the case for two nonionic surfactants, namely Brij-35 and Brij-22.

According the solid-state ^{13}C NMR analyses performed by Lavine et al. [56], the hydrophobic tail of the anionic surfactant SDS was found to be linked to the alkyl chains of the C18-stationary phase, while the sulfate polar groups were oriented away from it. Thereby, a top layer is negatively charged and affects the depth of penetration into the stationary phase.

The NMR-based model showing the structure of CTAB-modified stationary phase revealed that some trimethylammonium groups were attracted to oppositely charged free silanols. The remaining fraction of

Table 2
The selected characteristics of the most commonly utilized surfactants in MLC.

Name of surfactant	Chemical formula	CMC (mM)	Aggregation Number	Krafft Temperature (°C)	Molar volume (mol L^{-1})
SDS	$C_{12}H_{25}SO_4Na$	8.1	62	16	0.246
CTAB	$C_{16}H_{33}N(CH3)_3Br$	0.83	90	26	0.364
Brij-35	$C_{12}H_{25}(C_2H_4O)_{23}OH$	0.06	41	100>*	1.12

adsorbed monomers was protruded with its polar head towards the mobile phase. This finding explains the higher polarity of SDS-coated alkyl phases over CTAB-modified columns [56].

The amount of adsorbed surfactant monomers on the stationary phase decreases linearly with increasing alcohol content in the mobile phase. The mentioned phenomenon is a consequence of the competition of alcohol molecules and surfactant monomers for the same adsorption sites. It has been shown that the intensity of monomer desorption depends on the type of alcohol used. For SDS and CTAB, the magnitude of this effect is related to the hydrophobicity of the alcohol and follows the trend: methanol < ethanol < propanol < butanol < pentanol [57, 58].

3.1.2.2. The mobile phase. The micellar mobile phases contain micelles and surfactant monomers in aqueous solution (or hydro-organic mixture). Addition of organic solvent to the micellar mobile phase gives rise to a mode denoted as hybrid MLC. In the case of hybrid micellar mobile phases, molecules of organic solvent may be free or linked to a surfactant.

The organic solvent increases the hydrophobicity of the mobile phase and impacts the structure of the micellar aggregates. Regarding the latter, there are three possible options: Molecules of organic solvents can bind to the micelle surface, be placed in the palisade stratum or be inserted deep into the micelle's core. The pattern of behavior depends on the type of organic solvent. For instance, molecules of short-chain alcohol, such as 1-propanol, reside outside the micelles, which minimizes the electrostatic repulsive forces between the head groups (groups possessing charges of the same sign). Ultimately this support micelle formation and reduce the CMC value. At the same time, methanol and acetonitrile solvate the surfactant molecules, interfering with further formation of micelle aggregates and increasing the CMC. In addition to the CMC parameter, the surfactant aggregation number can also be altered under hybrid MLC conditions [59].

Besides mentioned organic solvents, the other short/medium chain alcohols are also preferably used. These solvents enhance the efficiency of the MLC technique thanks to a decrease in viscosity as well. The elution strength of organic modifiers is conditioned by their chain lengths. The content of the organic modifier in the mobile phase must be at a sufficiently low level to preserve the micelles' integrity. For instance, in SDS-induced MLC systems, the maximum content of methanol, acetonitrile, 1-propanol, 1-butanol and 1-pentanol is 30–40%, 30%, 22%, 10% and 7%, respectively. On the other hand, the presence of CTAB micelles was not observed in solutions containing methanol above 20%. More recently, higher amounts of organic solvents have been added to the mobile phase to disrupt micelles and yield good performance in the separation of cationic polar and apolar analytes. This chromatographic mode is called High Submicellar Liquid Chromatography (HSLC) [58].

3.1.3. Interactions in MLC (analyte–micelle and analyte–stationary phase interactions)

The MLC system is a sophisticated analytical system consisting of three microenvironments: stationary phase, bulk water or hydro-organic mixture (with surfactant molecules) and micellar pseudo-phase. Thus, variety of interactions can be observed; the analyte may externally bind to the micelles, may penetrate the palisade layer or the micellar core; it can interact with the adsorbed surfactant (either the non-polar tail or polar head) and with the stationary phase (non-modified part or the free silanols). The nature of the analyte and the nature of the system components determine the nature of interactions that occur in-between and, thus, control the MLC retention [60].

3.1.3.1. The nature of the interaction. It has been reported that neutral and charged analytes can experience hydrophobic, dipole - dipole and proton donor - acceptor interactions with nonionic surfactants. On the other hand, electrostatic interactions are commonly established between charged analytes and ionic surfactants. In both cases, steric effects may be relevant to the retention behavior of the compounds of interest. When it comes to the electrostatic interactions, analytes that are of the opposite sign to the sign of head group can be attracted by the surfactant, while analytes that have the same sign experience repulsive interactions. If repulsive interactions occur between the analytes and the charged surface of the stationary phase and/or the outer layer of the micelles, satisfactory retention is achieved only if the analyte forms hydrophobic bonds with the modified, alkyl-bound stationary phase. Otherwise, the analytes cannot remain retained on the stationary phase long enough and elute together with the mobile phase. The attractive interactions combined with the hydrophobic forces, in turn, can contribute to strong retention in the MLC system. Despite the complexity of MLC system, the great benefit of corresponding methods is reflected in their ability to simultaneously separate challenging mixture of polar and non-polar analytes [46].

3.2. MLC method development

In order to enable further progress in the application of MLC technique, it is necessary to facilitate the method development process. This seems to be a more challenging task than the development of classical LC methods due to a number of factors (e.g. type and concentration of surfactant and organic solvent, pH, temperature, etc.) that must be balanced to provide optimal separation of a multicomponent mixture. In this regard, it is of the utmost importance to develop a model that accurately describes the MLC retention mechanisms.

Despite the continuity of use, the most accepted theory regarding given retention mechanisms is still under debate. The early attempts to model analyte retention in MLC included the establishment of theoretical equations with a clear physicochemical connotation [53]. In fact, these models described the hyperbolic dependence of the retention factor, k' on the "micellar" concentration, $[M]$ (the difference between the total surfactant concentration and the CMC). Traditional retention models in MLC are summarized inTable 3. Armstrong and Nome were among the first to postulate that solute retention in a MLC system is partition-driven phenomenon and that analytes can be distributed between the aqueous phase, the micellar pseudo-phase and the surfactant-coated stationary phase (Eq. 9) [61], Arunyanart and Cline-Love, on the other hand, considered the MLC retention from the aspect of association equilibria. According to this theory, the binding constants, K_{AS} and K_{AM} (Eq. 10) govern the equilibria between the analyte in bulk solvent and the binding sites at the stationary phase (S), i.e. the surfactant molecules in the micelle (M) [62]. The equations 9 – 10 were successfully applied in case of versatile compounds, surfactants, and columns as stated in [45]. Founded on the concept that the association between the compounds in the solvent and the stationary phase was primary equilibrium affected by the association between the analyte and micelles (secondary equilibrium), Eq. 11 was established by Foley [63]. The equations 9 – 11 are quite similar and all predict a drop in retention

Table 3
Traditional retention models in MLC.

Model	Model	Parameters used	Ref.
Eq. 9 (Armstrong and Nome model)	$k' = \frac{P_{AS}}{1+\upsilon(P_{AM}-1)[M]}\ \varphi$	k' – retention factor of analyte at a fixed pH of micellar aqueous phase $[M]$ – micellar concentration (total surfactant concentration minus CMC) P_{AS} – the coefficient related to the partitioning of analyte between the stationary phase and aqueous phase P_{AM} – the partition coefficient of analyte between the micellar pseudophase and aqueous phase φ – the phase ratio υ – the partial specific volume of the monomers in the micelle	[61]
Eq. 10 (Arunyanart and Cline-Love model)	$k' = \frac{K_{AS}[S]}{1+\ K_{AM}[M]}\ \varphi$	K_{AS} – the binding constant between analyte and stationary phase (S – binding sites on the stationary phase) K_{AM} – the binding constant between analyte and the surfactant monomers in the micelle $[S]$ – the stationary phase activity	[62]
Eq. 11 (Foley model)	$k' = k\ \frac{1}{1+K_{AM}[M]}$	k – the retention factor of an analyte in the absence of micellar mobile phase	[63]
1 Eq. 12 (Model proposed by Khaledi et al.)	$logk' = logk\ - -S\varphi$	$logk'$– the logarithm of the retention factor in a hybrid MLC system $logk$ – the logarithm of the retention factor in a pure MLC system φ – the content of organic modifier in the mobile phase (%, v/v) S – the elution strength of a hybrid micellar mobile phase	[66]
1 Eq. 13 (Empirical model)	$\frac{1}{k'} = c_0 +\ c_1[M] + c_2\varphi +\ c_3\varphi[M]$	$c_0 - c_3$ are the fitting coefficients of the equation	[67]
1 Eq. 14 (Mechanistic interpretation of empirical model)	$k' = \frac{K_{AS}^{\varphi}}{1+\ K_{AM}^{\varphi}[M]}$	K_{AS}^{φ} – apparent constant related to the binding effect between analyte and the modified stationary phase (with respect to φ) K_{AM}^{φ} – apparent constant related to the binding effect between analyte and the micelles (with respect to φ)	[45]
1 Eq. (15) (Three-factor model)	$k' = \frac{k'_A + k'_{HA} + K_H^{M,\ \varphi}h}{1+\ K_H^{M,\ \varphi}h}$	k'_A – retention factor of basic structures k'_{HA} – retention factor of acidic structures $K_H^{M,\ \varphi}h$ – apparent constant that depends on the surfactant concentration and organic modifier content, as well as, on the association ability of acid-base species with the micelles h – the concentration of H^+	[46]

with increasing surfactant concentration. However, a parallel between the micellar pseudo-phase in MLC and the organic solvent in RP-LC can only be drawn for compounds that enter into certain associations with the surfactant (neutral compounds and structures of opposite charge). If analytes do not have the so-called binding character, their retention remains unchanged with the increase in the concentration of surfactant. Although least common, it has been observed that increasing the surfactant concentration prolongs retention for some analytes. Such analytes have an anti-binding nature (due to repulsive interactions with micellized surfactant as well as adsorbed monomers) [64] and the description of their retention requires adaption of above listed models [65].

However, equations 9 – 11 do not take into account many other factors important for analyte retention in MLC. In this regard, Khaledi et al. [66] modeled the drastic changes in retention behavior of analytes with respect to the varying content of organic modifier in the micellar mobile phase (Eq. 12). Given how the proposed linear relationship is attainable only in the case of methanol as an organic modifier, retention in the hybrid MLC system was further modeled on an empirical and mechanistic ground. The empirical model that had most success in describing the relationship between the retention factor of versatile solutes and the concentration of both surfactant and organic solvent among series of derived equations according to [67] is expressed by Eq. 13. Based on additional experiments, Jiménez et al. [45], however, argued that the relationship is rather quadratic for hydrophobic analytes and MLC mobile phases containing the n-butanol. Both groups of authors reported the worst results when the dependent variable was expressed as the logarithm of the retention factor. Mechanistic model that was later proposed is given by Eq. 14.

Modeling of the effect of three variables (Eq. (15)) was conducted to further improve the understanding of the underlying retention mechanisms and facilitate the optimization of the MLC separation of charged compounds. The non-contracted equation that describes the change in the retention factors of analytes with the variation in surfactant concentration, modifier content and pH is given in [46].

Over past decade, the computer-aided method development has gained popularity among MLC practitioners. Rodenas-Montano et al. [68] showed that DryLab software can be used to separate β-blockers in urine sample by optimizing the gradient of 1-propanol (at a constant concentration of SDS). Furthermore, application of chemometrics techniques, namely experimental design, in predicting the retention factors or other parameters that describe the chromatographic behavior of the analytes within a MLC system has been favored. For instance, Ramezani et al. [44] applied RSM to fine-tune the duration of MLC method and the separation of 4 antraquinone dyes. The authors achieved this goal

by optimizing four factors (the SDS concentration, the content of acetic acid, the type and the content of organic modifier) via Central Composite Design, CCD. Similarly, Safa et al. [50] applied Derringer's desirability function to simultaneously optimize the quality and duration of MLC separation of 9 phenyl thiohydantoin amino acids. To map the 3D chromatographic response surface, authors varied the concentration of SDS, the alkyl chain length of the organic modifier, the content of the organic modifier, the pH of the mobile phase and the column temperature according to face-centered CCD plan of experiments. DoE was also successfully employed in the mixed MLC analysis of norfloxacin and tinidazole, where the optimization of the SDS and Brij-35 concentration, as well as, the pH of the mobile phase was carried out by 2^3 full factorial design [69]. In the interesting study [70], stability-indicating micellar method (18 mM Brij L23, pH 3.8/13% acetonitrile) for the analysis of cilazapril, hydrochlorothiazide and their degradation products was established via AQbD and experimental design supplemented by a grid point search methodology. Both method development strategies ultimately ensured satisfactory separations of all examined compounds. The AQbD strategy, however, resulted in a better understanding of the MLC method and did not require additional evidence of the method robustness. On the other hand, the grid point search methodology defined a wider area of optimal conditions that had unreliable boundaries. On the basis of these findings, the authors proposed AQbD as the methodology of choice, noting that for sophisticated calculations (related to design space) there is no user-friendly software.

In addition to the above strategies, QSRR modeling is frequently adopted to understand retention mechanisms in micellar LC environments and, in particular, to accurately predict retention factors in order to effectively develop the MLC method. Being one of the first QSRR approaches with wide applicability and easy determination of a limited set of descriptors., the linear solvation energy relationship (LSER) modeling has been employed in numerous fundamental MLC-based studies [71–73]. For instance, Mutelet et al. [72] applied the LSER approach to correlate solvatochromic descriptors of 15 polyaromatic hydrocarbons with a retention factor ($\ln k$) in SDS-, Brij 35- and CTAB-mediated micellar LC (containing 2-propanol as the organic modifier). The most significant contributors to the observed retention seemed to be the size and basicity of the tested compounds with positive, i.e. negative trend towards $\ln k$. Furthermore, Torres-Lapasió et al. [74] critically discussed the applicability of the LSER approach for MLC analysis of ionisable compounds (mainly polyaromatic hydrocarbons, sulfonamides, β- diuretics, etc.) in hybrid and pure MLC systems induced by SDS, CTAB and Brij-35. In order to improve the accuracy of the proposed model, the authors added a correction term (in relation to ionic and steric interactions) to the original Abraham model. The authors stated that mentioned correction annulled the differences between the descriptors of neutral and ionic species. Recently, Ramezani et al. [75] established a simple, multiple linear relationship between the 5 molecular descriptors calculated by Dragon (log P, GATS8v, Mor27m, MATS7m, and JGI4) and the retention times ($\log t_r$) of 16 anthraquinones analysed under MLC conditions (120 mM SDS; 5% different organic modifiers; 4% glacial acetic acid). The authors argued that the developed model is of great predictive ability and that the selected descriptors carry aggregated information on the analytes' structural characteristics as well as the properties of the organic modifier (e.g. $\log P$). In a similar manner, Krmar et al. [76] correlated the retention factors ($\log k$) with both physicochemical, topological, spatial structural and quantum chemical properties of the test compounds (aripiprazole and its five impurities) and experimental variables (concentration of Brij L23, pH of the aqueous phase and the acetonitrile content in the mobile phase). In this regard, the authors established 48 QSRR models by combining 6 feature selection methods (Principal Component Analysis, Non-negative Matrix Factorization, ReliefF, Multiple Linear Regression, Mutual Info and F-Regression with 8 predictive algorithms (Linear Regressions, Ridge Regression, Lasso Regression, Artificial Neural Networks, Support Vector Regression, Random Forest, Gradient Boosted Trees and K-Nearest neighbourhood). Comparative analysis showed that different algorithms had great diversity in adapting to the data, among which GBT showed the best performance. Steric factors and dipole-dipole interactions were identified as the most important factors. The selection of logarithmic transformation was mathematically driven, rather than it had physicochemical background.

3.3. MLC applications

Number of MLC-related scientific documents published in the domain of drug analysis in the period 2012–2021 (226 papers found by Web of Science platform on November 2021) indicate that interest in a given chromatographic mode has not waned. Thus, we found it useful to analyze some of the recent applications of the MLC technique to gain insight into how it has evolved over time. As summarized inTable 4, in the last 5 years the MLC technique has been mainly utilized for isocratic separation of pharmaceutical compounds having widely different polarities and charges, such as β-blockers, sulfonamides, diuretics and tricyclic antidepressants. Reported studies generally include assays of active pharmaceutical ingredients in formulations and biological samples, but some methods for the analysis of drugs in food and in other type of matrices have been also established [44, 69, 70, 77-98].

The anionic SDS is, by far, the most frequently used surfactant in MLC pharmaceutical reports found over the 2017–2021 time period. This is probably due to acceptable costs, former experience and fact that it is available at high purity. Moreover, SDS acts as efficient suppressor of silanol activity of the column packing [99]. Also, in the case of biological samples, SDS is the surfactant of choice because it denatures proteins and, thus, releases associated drugs that are further available to interact with the stationary phase. Basically this means that physiological matrices can be simply injected into the SDS-based MLC system after the dilution and filtration steps [100]. Besides SDS, some of the reported MLC studies used non-ionic Brij-35 and cationic CTAB. The adequacy of SDS, Brij-35 and CTAB for MLC analysis may be the reason for the occasional interest in seeking out new surfactants with application in LC. In this regard, few papers investigated versatile surfactants in MLC, such as the zwitterionic surfactant n-dodecyl-N,N-dimethylamino-3-propane-1-sulfonate [101] and the phosphocholine-based lipid, miltefosine [102]. Biological bile salts (sodium cholate, sodium deoxycholate and sodium taurocholate) are also interesting non-traditional surfactants that lack a classical linear structure.

Most MLC analyses make use of hybrid micellar mobile phases. In this context, 1-propanol is the most common modifier of micellar solutions, but acetonitrile has also called considerable attention. When it comes to the analysis of highly lipophilic compounds, 1-butanol and 1-pentanol are often used organic solvents. To facilitate the selection of the type and content of organic solvent within SDS-induced MLC environment, Ruiz-Ángel et al. provided subsequent recommendations: only a small amount of propanol (≈ 1%, v/v) is sufficient to separate the analytes with $log P_{o/w} < -1$ (e.g. amino acids); a higher amount of propanol (≈ 5–7%, v/v) is necessary for analytes with $log P_{o/w}$ ranging from −1 to 2 (e.g. sulfonamides and diuretics); a large amount of propanol (≈ 15%, v/v) or small amount of butanol (< 10%, v/v) are beneficial in the analysis of less polar substances with $log P_{o/w}$ ranging from 1 to 3 (e.g. β–blockers). Pentanol (< 6%, v/v) is most useful for apolar structures with $log P_{o/w} > 3$ [59]. Boichenko et al. investigated aliphatic carboxylic acids as new modifiers of SDS micellar solvent. They observed that use of aliphatic carboxylic acids yielded better isocratic separation of 2,4-dinitrophenyl-amino acids on C18 stationary phase in comparison with traditional MLC modifiers, namely aliphatic alcohols [103].

A short time ago, several studies were carried out with the goal of replacing the organic solvent in the hybrid SDS-MLC with an additional surfactant. Accordingly, Brij-35 was considered first of all. The feasibility of mixed MLC approach is based on the competition of SDS and Brij-35 monomers for binding sites on the stationary phase i.e. reduced hydrophobicity of the stationary phase with preserved net charge. Also, SDS and Brij-35 appear to form mixed micelles [104], which generate

Table 4
Summarized applications of MLC technique in the domain of drug analysis (2017–2021).

Analytes	Sample	MLC system	Elution mode in hybrid MLC systems (and temperature)	Ref.
Enalapril maleate, lisinopril dihydrate, benazepril hydrochloride and hydrochlorothiazide	Pharmaceutical drug products	120 mM SDS, 10% 1-propanol, 0.3% TEA, 20 mM phosphoric acid (pH 3.6); Nucleosil 100–5 C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 25 °C	[77]
Metoprolol and amlodipine	Pharmaceutical drug product	100 mM SDS, 10% n-butanol, 20 mM sodium dihydrogen phosphate (pH 3.0); X-Bridge ODS column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 40 °C	[78]
Cilazapril and hydrochlorothiazide	Pharmaceutical drug product	18 mM Brij L23, 13% ACN, pH 3.8; XTerra RP 18 column (150 mm x 3.9 mm, 5 μm)	Isocratic elution, 30 °C	[70]
Free amino acids	Pharmaceutical drug product	75 mM SDS, ACN, acetate buffer (pH 3.5); Venusil XBP column (250 mm x 4.6 mm, 5 μm)	Gradient elution (25% to 60% in 30 min), 35 °C	[79]
Atenolol, celiprolol, metoprolol, oxprenolol and propranolol	Pharmaceutical drug products	150 mM SDS, 50 mM Brij-35; Zorbax Eclipse XDB column (150 mm x 4.6 mm, 5 μm)	25 °C	[80]
Antihypertensive drugs	Pharmaceutical drug products	80 mM SDS, 10.0 mM Brij-35, 10.0 mM sodium dihydrogen phosphate, (pH 5); Kinetex C18 column (150 mm x 4.6 mm, 5 μm)	30 °C	[81]
Diazepam, clonazepam and bromazepam	Pharmaceutical drug products	50 mM SDS, 10 mM Brij-35 (1:1), phosphoric acid (pH 7); Onyx™ Monolithic C18 column (100 mm x 4.6 mm)	25 °C	[82]
Norfloxacin and tinidazole	Pharmaceutical drug product	140 mM SDS, 30 mM Brij-35, 0.3% TEA, orthophosphoric acid (pH 2.9); ODS Hypersil (R) column (250 mm x 4.6 mm, 5 μm)	30 °C	[69]
Paracetamol, guaifenesin, pseudoephedrine, ibuprofen, chlorpheniramine, and dextromethorpha	Pharmaceutical drug product	93.6 mM SDS, 32.0 mM Brij-35, 10.0 mM sodium dihydrogen phosphate (pH 5.2); Kinetex C18 column (150 mm x 4.6 mm, 5 μm)	35 °C	[83]
Favipiravir	Pharmaceutical drug product/Human plasma	150 mM SDS, 20.0 mM Brij-35, 20.0 mM sodium dihydrogen phosphate, (pH 5.0); VDSpher 150® C18-E column (250 mm x 4.6 mm, 5 μm)	30 °C	[84]
Esomeprazole, leflunomide and ibuprofen	Pharmaceutical drug product/Human plasma	100 mM SDS, 10% n-propanol, 0.3% TEA, 20 mM orthophosphoric *aci* (pH 3.5); Shim-pack VP-ODS column (150 mmx 4.6 mm, 5 μm)	Isocratic elution, 25 °C	[85]
Tizanidine, Nimesulide, Aceclofenac and Paracetamol	Pharmaceutical drug products/Biological Fluids	120 mM SDS, 10% butanol, 25 mM phosphate buffer (pH 3.0); Shim Pack Cyano column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 40 °C	[86]
Levodopa, carbidopa and entacapone	Pharmaceutical drug product/Human plasma	100 mM SDS, 10% n-propanol, 0.3% TEA, 20 mM o-phosphoric acid (pH 2.8); VP-ODS column (250 mm x 4.6 mm, 5 μm)	Isocratic elution	[87]
Cabozantinib and its four major metabolites	Human serum	200 mM CTAB, 50% ACN, 10% tris buffer (pH 8.5); Kinetex C18 column (100 Å)	Isocratic elution, 35 °C	[88]
Rifampicin and rifabutin	Human plasma	150 mM SDS, 6% 1-pentanol, phosphate buffer (pH 3.0); Kromasil 5 C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 25 °C	[89]
Isoniazid and pyridoxine	Human plasma	150 M SDS, 8% 1-butanol, 10 mM phosphate buffer (pH 3.0); Kromasil 5 C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 25 °C	[90]
Citalopram hydrobromide and its two demethylated metabolites	Biological samples	180 mM SDS, 15% 1-propanol, 0.3% TEA, 200 mM o-phosphoric acid (pH 4.0); Prontosil Kromaplu C18 column (250 mm x 4.6 mm, 5 μm)	Isocratic elution, 60 °C	[91]
Rivaroxaban	Plasma and urine	50 mM SDS, 12.5% 1-propanol, phosphate buffer (pH 7.0); Kromasil C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution	[92]
Axitinib, lapatinib and afatinib	Plasma	70 mM SDS, 6% 1-pentanol, 10 mM phosphate salt (pH 7.0); Kromasil C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution, 25 °C	[93]
Sulfonamides	Medicated feed	50.0 mM SDS, 6% propan-2-ol, 20 mM phosphate buffer (pH 3.0); Zorbax Eclipse XDB C18 column (150 mm x 4.6 mm, 5 μm)	Isocratic elution	[94]
Mebendazole	Dairy products and animal nitrogenous waste	150 mM SDS, 6% 1-pentanol, phosphate buffer (pH 7.0); SPHER-100 C18 100A column (250 mm x 4.6 mm, 5 μm)	Isocratic elution	[95]
Alizarin, purpurin, danthron, and quinizarin	Natural antraquinone dyes	90 mM SDS, 10% ethanol-propano (1:1), 4% ACA; C18 ODS Knauer analytical column (125 mm × 4 mm, 5 μm)	Isocratic elution, 25 °C	[44]
Paracetamol and impurities p-amino phenol and p-nitro phenol/ Pseudoephedrine hydrochloride and impurities benzaldehyde and benzoic acid	Pharmaceutical drug products - 2 dosage forms	100 mM SDS, 10% acetonitrile, 0.3% TEA,	Paracetamol and impurities p-amino phenol and p-nitro phenol/ Pseudoephedrine hydrochloride and impurities benzaldehyde and benzoic acid	[96]
Bambuterol and its main degradation product, terbutaline	Pharmaceutical drug products	100 mM SDS, 15% n-propanol, 0.3% TEA, (pH 3.5);	Bambuterol and its main degradation product, terbutaline	[97]
Hydrocortisone acetate, pramoxine hydrochloride and their impurities	Pharmaceutical drug products	150 mM SDS, 10% n-propanol, 0.3% TEA, 20 mM o-phosphoric acid (pH 5.00); Eclipse XDB-C8 column (150 mm x 4.6 mm, 5 μm particles)	Isocratic elution	[98]

a different peak shape, compared to that observed with pure micellar solutions. In order to examine the adequacy of the given approach for challenging lipophilic compounds, Peris-García et al. [80] compared retention, resolution and peak shape of five common β-adrenoceptor antagonists (atenolol, metoprolol, propranolol, oxprenolol and celiprolol) obtained with mixed micellar (SDS/Brij-35) solution to retention behavior observed in the hybrid MLC (SDS/1-propanol) system. It was shown that separation of cationic analytes was excellent under optimal conditions (0.15 M SDS/0.05 M Brij-35 and 0.11 M SDS/10% 1-propanol) in both systems. However, propranolol and oxprenolol had prolonged retention with the hybrid MLC mobile phase (> 20 min). On the other hand, the mixed mode suffered from somewhat wider peaks. While the elution order for the tested compounds was the same using both MLC modes, some differences in selectivity were apparent.

In most contemporary MLC procedures, the pH value is set between 3 and 4. As for weak acids, the given values favor protonated species, thus providing better possibilities for their separation. Manipulation of pH within the operating range of conventional RP-LC stationary phases generally does not affect the retention of bases. Nevertheless, even in the case of drugs with basic properties, a low pH is usually set in order to increase the column efficiency.

Most contemporary MLC methods include conventional C18 columns. It was concluded that the pore size of conventional columns played an important role in the MLC behavior of analytes. Basically, the weak strength of micellar solutions is likely a consequence of the inability of micelles to penetrate the pores of the stationary phase, within which the analytes reside most of the time. Thus, even a high concentration of either nonionic or ionic surfactant cannot elute lipophilic compounds, since micelles have access to the analytes only when they are diffused out of the pores [105]. To investigate whether this issue can be addressed with wide-pore columns, McCormick et al. compared the retention of analytes with differing polarity and size on several columns in the range from 100 to 4000 Å. They found that packing materials with larger pore sizes enhanced the eluting strength of the MLC mobile phases. Although this was considered true for all types of surfactants, the greatest effect was observed with non-ionic surfactant [105]. In addition to conventional RP-LC columns, there are examples in the literature of MLC experiments performed using slightly different types of stationary phases. For instance, El-Shaheny et al. [106] considered three different columns for the separation of flavoxate HCl and its degradation products within the SDS-induced micellar environment. Among the CLC Shim-pack C_8 column, CLC Shim-pack CN column and BDS Hypersil phenyl column, the latter proved to be the most appropriate because it successfully resolved all the peaks in a short run-time. On the contrary, the more conventional C8 column strongly retained the highly lipophilic active substance. Similarly, the cyanopropyl column gave an asymmetrical broad peak of API that overlapped with the degradation product and, therefore, was also not suitable for the intended purpose.

As provided, most MLC-based separations run at a constant level of organic modifier. The isocratic mode is so readily used because MLC conditions allow an even distribution of the analytes in the chromatograms. This phenomenon is similar to the gradient elution effect in classical RP-LC, but with a clear advantage of waste reduction. However, Ke et al. [79] proved that an efficient surfactant-based gradient LC method can be useful for quantitative analysis of free amino acids. This procedure makes progress from the MLC mode to the submicellar LC environment, leading to altered elution strength, peak shape and selectivity. Gradient elution in MLC analysis of physiological fluids was especially promoted by Rodenas-Montano et al., stating that the initial low content of the organic modifier better protected the column against the proteins of biological matrix, while the consequent higher content of organic solvent reduced the method duration [68].

As mentioned earlier, the MLC technique allows the determination of API(s) from different complex matrices without the help of an extraction processes. In this regard, it is very gladly used in the analysis of stress samples as shown in the literature [96, 97, 106-109]. Moreover, MLC stability-indicating methods are favorably used in this field because they successfully separate compounds that carry different charges, i.e. neutral species with diverse polarities in a single run and without the introduction of a gradient elution program.

In an interesting study [98], Ibrahim et al. compared the performance of two methods, namely RP-LC and MLC, developed for the simultaneous determination of hydrocortisone acetate, pramoxine hydrochloride and their impurities . Both methods turned out to be precise, accurate and robust. Even though the RP-LC method outperformed the MLC method in terms of efficiency and sensitivity to impurities, the authors highlighted the resources rationalization that was exclusively related to the use of MLC. The developed MLC method showed satisfying green character by separating 4 analytes using only a small amount of organic solvent. In addition, it separated the drugs in the combined cream without prior sample treatment, which condensated the time of the procedure and the amount of toxic solvents.

Similarly, Otašević et al. [70] proposed the MLC method to overcome the shortcomings of the initially developed RP-UHPLC method for the analysis of cilazapril, hydrochlorothiazide and their impurities. Pointing out that (U)HPLC methods with gradient elution are vulnerable to influence of various parameters (e.g. gradient profile, column geometry, flow rate of the mobile phase, column equilibration time between gradient runs, ghost peaks, etc.), the authors aimed to develop a new stability-indicating method with an isocratic elution mode for the analysis of compounds of interest. The MLC responded perfectly well to this non-trivial analytical challenge. The representative chromatogram of all analytes tested under the optimal MLC conditions (Figure 4) clearly testifies to the quality of the secondary developed MLC method.

The MLC technique has also come to attention in the Quantitative Structure – Property Relationship (QSPR) studies. Particularly, Brij-35 has been in the QSPR focus due to its ability to simulate the biopartition behavior of versatile drugs quite well [110, 111]. Tsopelas et al. [111] provided an insight into the potential of the Brij-35 mediated MLC system for modeling pharmacokinetic processes. Based on the analysis of 88 structurally diverse analytes, the authors concluded that retention factors can be used to model permeability, oral absorption and plasma protein binding.

Aforementioned bile salts have additional interesting use within MLC framework. Because bile salts possess several chiral centers, they can be utilized as chiral mobile phase additive (CMPA) in RP-HPLC [112]. After the thalidomide catastrophe, chiral APIs started to be developed as a single enantiomer. This led to labeling a minor enantiomer as a major impurity. The HPLC enantiomer separation of pharmaceuticals employing bile salts is recognized as quite effective [113]. The chiral recognition ability of bile salts namely, cholic acid and taurodeoxycholic acid sodium salts, as single selectors or as dual selectors was tested in HPLC and CE for model substances 1,1′-binaphthyl-2,2′diyl hydrogenphosphate and 1,1′-bi-2-naphthol. These model substances are very important because they have been widely used in organic enantioselective synthesis as building blocks in catalysts. Under the HPLC conditions studied, cholic acid sodium salts acting singly enable the separation of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate enantiomers, while 1,1′-bi-2-naphthol enantiomers weren't resolved under HPLC conditions. Chiral recognition ability of each selector separately has been investigated and cholic acid and taurodeoxycholic acid sodium salts were adsorbed on the stationary phase at relatively high coverage, but its concentrations both at the stationary phase and in mobile phase remains unknown. The mechanism of separation for tested enantiomeric pairs is complicated to explain because many routes could play main role, like complexation equilibrium, micelle formation in solution and on the stationary phase and mixed adsorption processes on the stationary phase. For 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, it could be observed that it is more favorable for the S than for the R enantiomer to intrude into the micelle adsorbed on the stationary phase. The use of mixed system composed of two different chiral principles, bile salt and cyclodextrin, lead to the conclusion that there is no advantage in

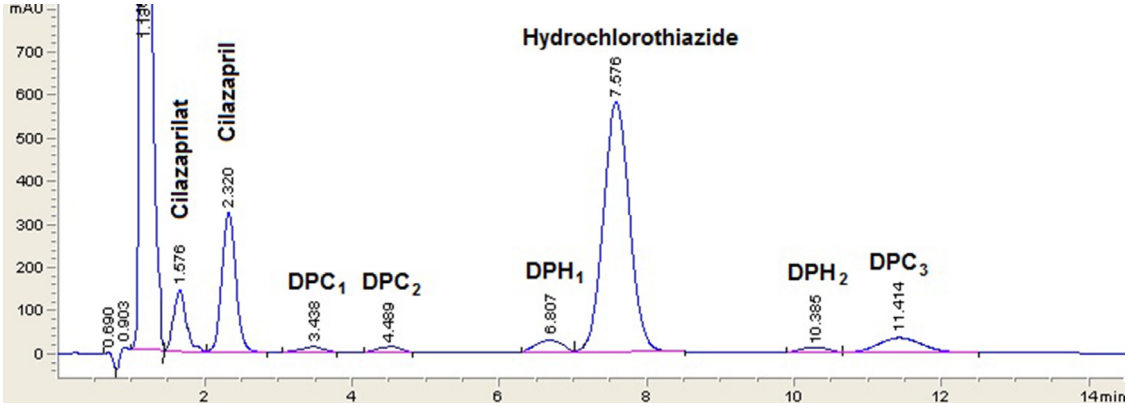

Fig. 4. The chromatogram of cilazapril, hydrochlorothiazide and their degradation products acquired under optimal MLC conditions (18 mM Brij L23, pH 3.8/13% acetonitrile) [70].

comparison to the single systems and or makes it worse resolution between enantiomeric pair (or even destroys it) [114]. Five different non-ionic surfactants (Brij 35, Brij 56, Triron X-100, Tween 20 and Tween 60) were tested as mobile phase modifiers in chiral ligand exchange (LE) chromatography for separation of racemic mixtures of the amino acids DL-methionine, DL-leucine, DL-valine and DL-tyrosine. The role of surfactants was not to be chiral selector in system, but this paper will be included into this review because present utilization of micellar chromatography for separation of enantiomers. Among them, ionic surfactants (SDS and cetyl trimethylammonium bromide) were also used, but the separation of racemic amino acids was disturbed due to the very strong electrostatic interactions. Chiral additive was the copper (II) complex of N,N dimethyl-l-phenylalanine, and LE mechanism represent the one with the high enantioselectivity power for separation of amino acids. The main objective of this study was to examine the effect of surfactant concentration on process parameters like retention and selectivity. Change in the concentration of the micelles enables the control of the retention factors and the selectivity and in general no negative influence on the separation (due to surfactant adsorption on the non-chiral stationary reversed RP-C8 phase) occurred. The partition coefficients of the amino acid complexes between the aqueous phase and the micelles and between the micelles and the stationary phase were calculated with changes for surfactant concentration for Brij 35 using Armstrong model. It can be concluded that structure of the surfactant plays a major role for the distribution of the diastereomeric complexes between the mobile and the stationary phase and the selectivity of the substances. Elution order was not under the influence by the presence of surfactants [115]. Research group of authors Alwera et al. have published several papers on the subject of new approach using surfactant based mobile phase on RP-HPLC, without use of organic solvents. As such, this approach has characteristics of greenness of analytical method. Aim of these studies was to separate enantiomers of various substances (mainly β-adrenolytics and amino acids) using indirect approach in chiral chromatography, precisely derivatization of mentioned substances with chiral selector. As chiral selectors were used enantiomerically pure highly reactive chiral derivatization reagent based on (*S*)-(–)-levofloxacin, (*S*)-ketoprofen or (*S*)-ibuprofen-based activated esters. Diastereomeric derivatives of test substances were thus obtained microwave conditions and separated using achiral RP-column and achiral surfactant (SDS and Brij-35) based mobile phases [116–120].

4. CD-modified RP-HPLC

4.1. Theoretical background

CDs are cyclic oligosaccharides obtained by enzymatic degradation of starch. They are comprised of several D-glucose units linked with α−1,4 glycosidic bonds. Each glucose unit is in the rigid chair conformation, while together are forming a shape of a particular truncated conical cylinder, with the secondary hydroxyl groups located on the wider rim and the primary hydroxyl groups placed on the narrower rim. The H-3, H-5 and glycosidic oxygen are located inside the relatively hydrophobic cavity, while H-1, H-2, H-4 and H-6 protons are outside the cavity, forming a hydrophilic outer environment [121]. The aforementioned hydrophilic surface accounts for CD's solubility in aqueous solutions, while lipophilic cavity is able to accommodate wide variety of hydrophobic organic compounds including acids, bases and chiral substances [122–124]. Organic molecules are completely or partially encapsulated within the cavity, thus inclusion complexes are formed [122, 124-126]. The process of inclusion complexation depends on the fit of a whole or part of a guest molecule into the host cavity and it is determined with the complementarity in size and geometry between the guest molecule and host CD cavity. CD cavity is characterized by its height and internal diameter determined by the number of glucose units. Among native CDs, the cavity of α-CD is smaller in comparison to β-CD and γ-CD. For that reason, α-CD cavity is compatible with low molecular weight compounds with aliphatic chains, while β-CD accommodates well heterocyclic and aromatic compounds and γ-CD complex macrocycles and steroids. Although the structure of β-CD is the most rigid one in relation to other native CDs, its usage prevails the usage of other native CDs in pharmaceutical formulations, since most pharmaceutical active compounds have heterocyclic and/or aromatic structures [126]. In order to accomplish the inclusion complex formation, it is necessary to galvanize the equilibrium transfer into the direction of inclusion complex formation. This could be prompted by an extrusion of water molecules from the hydrophobic CD cavity, formation of hydrogen bonds with supplanted water molecule, reduction of repulsive interactions between the guest molecule and aqueous surrounding or increase in hydrophobic interactions upon entrance of guest molecule into the CD cavity [126–128]. Various kinds of non-covalent, mostly hydrophobic interactions occur between guest molecule and CD cavity upon inclusion complex formation process, ranging from van der Waals interactions to hydrogen bonds, dipol-dipol interactions and London dispersion forces. Generally, it is very difficult to predict the type and number of interactions involved in complex formation, therefore it is not easy to estimate the stability of the formed inclusion complex, which would be very helpful when choosing the right CD type with respect to structure of guest molecule [129, 130]. There are methods used to induce the inclusion complex formation, such as co-precipitation, slurry, paste and dry mixing, damp mixing, heating and extrusion methods. However, the process of inclusion complex formation is in most cases spontaneously driven. Water is a significant factor, representing the driving force for complexation, and should be a part of the medium in which both CD and analyte are dissolved. Additionally, water could be essential in maintaining the

integrity of the formed inclusion complex. Water is not only important when dealing with solutions, but also with crystal forms of the complexes, where they can form a bridge between the hydroxyl groups of the adjacent molecules of the CD [125, 129].

When discussing about water solubility, formed inclusion complexes show higher solubility in water in comparison to free organic molecules, hence CDs play an important role in different areas of pharmacy [126]. Apart from its widespread usage in industry [126], CD has an important role in analytical chemistry, especially in liquid chromatography, where they can be used as both mobile and stationary phase modifiers. If used as mobile phase additives, they are lowering the consumption of toxic organic solvents on the basis of inclusion complexes formation. In this way, applying CDs as mobile phase additives in liquid chromatography is recognized as one of the available strategies for developing ecologically acceptable liquid chromatography methods. Additionally, CDs' semi-natural origin and desirable non-toxicity makes them favorable additives in greener liquid chromatography [6, 131].

4.1.1. CD-modified RP-HPLC systems

Reversed-phase high performance liquid chromatography (RP-HPLC) systems modified with an addition of CD in the mobile phase are dynamic and rather complicated, because the examined analyte could be distributed between the stationary phase, mobile phase and CD dissolved in the mobile phase [124]. Also, free CD could be adsorbed onto the stationary phase surface, forming in this way the so-called pseudo-stationary phase, which additionally complicates the retention mechanisms in CD-modified RP-HPLC system [132]. As previously mentioned, the use of β-CD is preferred over other native CDs when dealing with pharmaceutical compounds, since β-CD is able to accommodate most heterocyclic and aromatic compounds. Moreover, it is easily washed from the chromatographic column, since is it usually weakly adsorbed onto the surface of C18 stationary phase. Therefore, it is beneficial in terms of column's life. Throughout the literature, when assessing the apparent stability constants of inclusion complexes formed with various drug molecules, both native and modified β-CDs are mostly applied [133–135]. Developing new derivatives of CD gained interest among researchers because of their attractive characteristics. Modifying hydroxyl groups on the rim of the CD molecule often leads to improvement in solubility, possibility for secondary interactions, changed cavity hydrophobicity and the potential for analysis of highly hydrophobic and uncharged compounds [136]. Modified CDs harvest improved chiral selectivity for specific guest molecules, which broadens its practical utility and justifies an increased price in comparison to native CDs.

Upon the addition of CDs to the mobile phases, the secondary distribution equilibrium is forming, which can afford important advantages in terms of chromatographic separations. Although mentioned previously, it could be summarized as reduction in the analysis duration due to increased solubility of the analytes in the mobile phases, decrease in the retention factors and enhancement in selectivity on the basis of diverse affinities to the CDs. All these factors together provide substantial reduction in the consumption of organic solvent per chromatographic run. However, a potential drawback arises from limited compatibility with MS detection, which is an issued with mainly all other mobile phase additives [137].

The possibility of forming multiple interactions between the examined analyte and remaining components of chromatographic system is contributing to the complexity of CD modified RP-HPLC systems. Resolution and separation efficiency is under the influence of different experimental conditions, such as type and concentration of applied CD, mobile and stationary phase characteristics, as well as column temperature. As aforementioned, the release of surrounding enthalpy rich water molecules from CD cavity is leading the inclusion complex formation. These water molecules are supplanted with more hydrophobic molecules, thus energetically more favorable non-polar interactions are established. Up to now, there are many studies performed with an aim of revealing the structure of inclusion complexes and explaining the retention behavior in CD-modified RP-HPLC systems [131, 138, 139]. However, it is still not completely understood which retention mechanisms would lead the retention in these kinds of chromatographic systems. Recent study revealed the pronounced effect of molecular structure, shown through significant molecular descriptors, on retention. The groups located approximately 7.5 Å from the molecule's geometrical center and their steric factors are essential for the formation of inclusion complexes and consequently influence the retention. Retention behavior is greatly affected by the molecular size and shape, as well as analyte's lipophilicity. Also, the size and lipophilicity of the employed CD should not be neglected, because the stability of the formed complexes depends on the structural fit between the CD and examined analytes [140].

4.2. Modeling the relationship between analyte's structure and its retention in CD-modified RP-HPLC

The concept of QSRRs methodology was led by an idea to predict chromatographic behavior on the basis of molecular structure. Prior to QSRRs, the Quantitative Structure-biological Activity Relationships (QSARs) methodology was developed, so the same pattern of thinking was applied to the analysis of chromatographic data [141]. The QSRRs represent mathematical relationships between chromatographic parameters determined for a series of analytes in a given chromatographic system and numerical values accounting for structural differences between the investigated analytes, denoted as molecular descriptors [28, 142].

Classical QSRR approach relates only molecular descriptors to the selected response. In that respect, experiments are not conducted under variable experimental conditions, which constrains the practical applicability of the model and reduces its usage to the concrete values of parameters [20]. Therefore, the so-called mixed modeling relating both experimental parameters and molecular descriptors to the selected response took the lead, since in this way the model's predictive performance has been increased [143]. A step further has been made when dealing with CD-modified RP-HPLC systems. Being additionally complicated by the joint effect of complexation and adsorption equilibrium on retention behavior, a separate methodological approach for retention modeling is required. The influence of inclusion complexes on the retention induced the necessity for additional type of descriptors, the so-called complex association constants. Complex association constants as individual inputs of QSRR together with molecular descriptors and experimental parameters, were firstly mentioned in the paper published by Maljurić et al. [144].

The literature surveillance brought up different studies dealing with developing computational models with an aim of explaining CD complexation and retention behavior. Steffen et al. developed QSPR models predicting Gibbs free energy (ΔG°), enthalpy (ΔH°) and entropy (ΔS°) of CD complexation with different guest molecules[145]. The QSPR models were built with principal component regression (PCR), partial least squares regression (PLSR) and support vector machine regression (SVMR) and their abilities to accurately predict three thermodynamic parameters were evaluated. The strong dependence of ΔS° to the structure of inclusion complex explains its poor predictability [145]. Further, Katritzky et al. built QSPR models, which are able to predict free energies of complexation between guest molecules and CDs employing fragmental descriptors and CODESSA-PRO program. CODESSA-PRO utilizes different geometrical, topological, quantum chemical and thermodynamic molecular descriptors derived from molecular structural, which precludes the need for performing the experiments [146]. However, the drawback of CODESSA descriptors is its difficult interpretation, which is not the case with fragmental descriptors. Nevertheless, a physical phenomenon occurring during interactions leading to complexation can be a good basis for selecting the fragments for modeling [147]. Perez-Garrido et al. constructed regression-based QSPR model to predict stability constants of inclusion complexes between 233 organic compounds and β-CD [147]. TOPS-MODE descriptors were correlated with β-CD complexation

ability for the first time and it was concluded that hydrophobicity and van der Waals interactions represent the leading forces in complexation. In that respect, hydrophobic groups and voluminous species in the guest molecule structure are supporting the β-CD complexation [147]. Ghasemi et al. investigated host-guest interaction in complexation process [148, 149], while Ahmadi et al. developed a 3D-QSAR model with an aid of Grid INdependent Descriptors (GRIND). Genetic algorithm was used to select significant descriptors, which were then correlated to stability constants of complexes formed between 126 organic compounds and β-CD using PLSR. The stability of the formed complexes with β-CD is affected by the size and shape of the complexed guest molecules [150]. The study results highlighted steric and hydrophobic interactions as the main driving forces in β-CD complexation. In another study Ghasemi et al. constructed QSAR models which predicted complex stability constant of mono and 1,4-di-substituted benzenes with α-CD applying methods of comparative molecular field analysis region focusing (CoMFA-RF) and VolSurf. The combination of CoMFA fields with physicochemical descriptors enabled the improvement of the model's predictability [151]. The inclusion complexation of benzene derivatives with α-CD appeared to be mostly affected by electrostatic and hydrophobic effects, as well as molecular shape [151]. Li et al. modeled β-CD binding behavior of structurally diverse molecules characterized by poor solubility. They used complex stability constant values available in the literature and established a model with an aid of multiple linear regression [152]. Again, the hydrophobic effect was the most prominent factor in drug β-CD binding. In general, higher drug hydrophobicity led to higher values of complex binding constants. Developed *in silico* model elucidated the most important driving forces in the complexation process, namely hydrophobic interactions, electrostatic interactions, van der Waals interactions and hydrogen bonding [152]. Hydrophobic interactions and van der Waals interactions are the main driving forces in the process of binding, while hydrogen bonding and electrostatic interactions act as stabilizers of the formed inclusion complex by establishing and maintaining the binding and dissociation equilibrium. However, in order to generalize the presented conclusions, the dataset size should be increased. Also, there is a skewed distribution of the observed stability constant values, so R^2 values are relatively lower if comparing them to similar models found in literature [147, 152]. As the time frame is always an issue. Veselinović et al. used SMILES attributes, as a representation of the molecular structure, to preclude the calculation of the optimal geometry of molecules prior to model development [153]. The study results showed that Monte Carlo method is a promising computational method in QSPR model development. A few years later, SMILES strings were used in combination with non-linear MARSplines (multivariate adaptive regression splines) methodology to quantify the stability constant values of a variety of molecules towards β-CD [154]. The hydrophobic nature of CD cavity together with hydrophobic effect confirmed its importance, as in most of the aforementioned papers. Apart from predicting the affinity of guest molecules to β-CD cavity, the developed QSPR model could be applied to classify the compounds into types according to Biopharmaceutical Classification System, since it is known that permeability of the drug is affected by its hydrophobicity [154]. Šoškić et al. reported the development of QSPR models relating physicochemical and structural attributes to retention factors of 31 indole derivatives in HPLC. Stationary phase comprised of immobilized β-CD, thus inclusion complexes are mainly formed between examined analytes and stationary phase [155]. The joint influence of hydrophobic interactions and hydrogen bonds formed between β-CD in the stationary phase and indole derivatives is determining the complex stability constants.

On the other hand, Maljurić et al. reported the development of QSRR model in RP-HPLC when β-CD is used as mobile phase additive. β-CD complexation process was analysed using the model mixture comprising of risperidone and its related compounds, as well as olanzapine and its related compounds. Although QS(P)RR methodology has been extensively used in characterizing β-CD complexation with various compounds, Maljurić et al. were the first to use molecular descriptors, complex associations constants and experimental parameters simultaneously as QSRR model inputs. Introducing complex association constants as QSRR model inputs contributed to the overall predictive power of the developed models [131]. In continuation of the previous research, Maljurić et al. applied the developed QSRR model to predict the change in retention factor's value upon complexation and consequently calculate stability constants and accompanying thermodynamic parameters of complexation [156]. QSRR model suggested that complex stability constants could not be determined on the basis of retention factor change under broad range of experimental conditions. This was also confirmed with experimental approach, which supports the validity of the QSRR modeling [156]. Further, this QSRR model was enriched with large pool of theoretical descriptors to ensure that all structural characteristics important for complexation are taken into account [157].

4.3. Application – literature preview

Number of papers dealing with application of CD in chromatography in the domain of drug analysis in the period of 2012–2021 (306 papers found by Web of Science on November 2021) reflects the substantial interest in this field, which lasts for decades. However, although extensively investigated CD-modified chromatography still offers many unanswered questions. Table 5 summarizes the papers published in the field of application of CDs as mobile phase additives in the previous five years [131, 158-170]. It can be roughly seen that it is either used for chiral recognition or development of greener liquid chromatography methods. Extraordinary properties associated with semi-natural origin and reasonable price are justifying its widespread usage.

4.3.1. CD as mobile phase additive in greener liquid chromatography method development

Greening liquid chromatography can take many forms, among which a recognized strategy includes using nontoxic mobile phases. It is well known that mobile phase in RP-HPLC consists of the aqueous part and organic solvent, most frequently acetonitrile or methanol. Greening could be directed towards changing the organic solvents with greener alternatives, such as ethanol and/or acetone or using mobile phase additives [171]. The use of CD as mobile phase additive induces a secondary distribution equilibrium, which can cause many benefits for chromatographic separation, in terms of reduced total run time on the basis of increased solubility of analytes, decrease in retention factor values and/or enhancement of selectivity due to varying affinities of analytes towards CD [137]. Adding CD to the mobile phase allows for an increase in the proportion of the aqueous phase without loss in the resolution or efficiency of separation [6].

Eco-friendly method for separation of five catechins was developed by Bi et al. with an addition of β-CD to the mobile phase. Adding β-CD allowed for efficient baseline separation with only 12% (v/v) acetonitrile in the mobile phase [172]. In the paper published by Maljurić et al. adding β-CD to the mobile phase enabled separation of risperidone and its related compounds in the total run time 3 min shorter comparing to the method without β-CD in the mobile phase with only 17.5% (v/v) of acetonitrile, which can be seen in the chromatogram published in the aforementioned paper. Moreover, total run time for separation of olanzapine and related impurities was approximately 8 min reduced if applying β-CD as mobile phase additive [131]. Recent study reported green stability indicating method for simultaneous determination of two anti-glaucoma drugs used as combination therapy in pharmaceutical dosage forms. Besides using ethanol as organic modifier, β-CD was added to the aqueous phase, contributing to the ecological acceptability of the method [158]. The paper published by Gonzalez-Ruiz et al. [6] illustrates the ability of β-CD and hydroxypropyl-β-CD for achieving greener RP-HPLC separations. Modified mobile phases en-

Table 5
Summarized applications of CD-modified RP – HPLC in the domain of drug analysis (2017–2021).

Analytes	Sample	Chromatographic system	Elution mode and column temperature	Ref.
Risperidone and its three impurities / Olanzapine and its two impurities	Bulk/Pharmaceutical drug product	Chromolith RP-18e (100 mm × 4.6 mm, macropore size 2 μm, mesopore size 13 nm), mobile phase for risperidone and impurities assessment: acetonitrile:aqueous phase (pH 2.4; 10 mM β-CD) (17.5:82.5, v/v); olanzapine and its impurities: acetonitrile:aqueous phase (pH 5; 10 mM β-CD) (22:78, v/v)	Isocratic elution, 35 °C	[131]
Four sesquiterpenoids (germacrone, curzerene, furanodiene, and β-elemene)	Oil of Curcumae Rhizoma	InertSustain C18 column (250 mm x 4.6 mm, 5 μm particles), mobile phase consisted of methanol and water (90:10, v/v), in which methyl-β-CD was dissolved with different concentrations ranging between 0 and 15 mmol L^{-1}.	Isocratic elution, 25 °C	[166]
Asiatic acid, madecassic acid, asiaticoside, madecassoside and asiaticoside B	Centella asiatica	Inertsil ODS C18 column (250 mm × 4.6 mm, 5 μm), mobile phases consisted of acetonitrile and 0.2% phosphoric acid solution containing 0.0, 1.0, 2.0, 4.0 or 6.0 mM CDs (α-CD, β-CD, HP-β-CD, Glu-β-CD or γ-CD)	Isocratic elution	[170]
Timolol, latanoprost and impurity LTN C3-epimer	Pharmaceutical drug product	Chromolith® Performance RP-18e (100 mm x 4.6 mm), mobile phase consisting of mixture of aqueous phase (containing 11.35 g β-CD and 1.5 g sodium octane sulfonate/L) and ethanol	Gradient elution, 35 °C	[158]
Tedizolid phosphate and S-enantiomer	Drug substance	Phenomenex Luna, Phenyl-Hexyl column (250 mm x 4.6 mm, 5 μm particles), mobile phase consisting of a mixture of aqueous buffer (pH 7.0) of disodium hydrogen phosphate with additive β-CD, triethylamine and acetonitrile	Isocratic elution, 20 °C	[159]
Amphetamine and its derivatives	Self-synthesized compounds	LiChrospher 100 RP-18e column (250 mm x 4 mm, 5 μm particles), mobile phase consisted of 2% sulfated β-CD in water (pH 6.0):methanol (97.5:2.5)	Isocratic elution, ambient temperature	[160]
Racemic mandelic acid	Cosmetic sample	Phenyl column and a mobile phase composed of 10 mM ammonium acetate buffer (pH 4.2) and 0.02% (v/v) HP-β-CD after passage of 10 mM ammonium acetate buffer (pH 4.2) containing 0.1% (w/v) HP-β-CD through a phenyl column at a flow rate of 1 mL/min for 60 min	Isocratic elution, 40 °C	[161]
Racemic metoprolol	Bulk	Two C18 columns, Zorbax Eclipse XDB C-18 column (15 cm x 10 mm, 10 µm) and Syncronis C18 HPLC column (250 mm x 4.6 mm, µm), mobile phase consisting of a mixture of aqueous solution (3.5 g M-ß-CD in 300 ml H_20), methanol with a volumetric ratio of 86:14 (v/v)	Isocratic elution	[162]
Nine indanone and tetralone derivatives	Standard substance	BDS C18 column (200 mm x 4.6 mm, 5 μm particles), mobile phase: a mixture of methanol and 0.05 mol/L phosphate buffer at pH 1.8 (55:45, v/v) containing 22.9 mmol/L CM-β-CD.	Isocratic elution, 25 °C	[163]
Oleanolic acid and ursolic acid,	Chinese herbal medicines	Agilent 5 HC –C 18 column (250 mm × 4.6 mm, 5 μm), mobile phase was composed of 0.5% ammonium acetate containing 40 mmol/L of hydroxypropyl-β-cyclodextrin and acetonitrile (30:70, v/v)	Isocratic elution, 15 °C	[164]
Maslinic acid and corosolic acid	Eriobotrya japonica (Thunb.) leaves	H&E SP ODS-A C18 column (250 mm × 4.6 mm, 5 μm), mobile phase was composed of methanol and 0.10% phosphoric acid with different concentration of hydroxypropyl-β-cyclodextrin (86:14, v/v) (pH 2.22)	Isocratic elution, 25 °C	[165]
Mandelic acid, 4-methoxymandelic acid and 4-propoxymandelic acid	Standard substance	XBridge™ C18 column (250 mm x 4.6 mm, 5 μm), the mixture solution of acetonitrile and 0.1 mol L^{-1} PBS containing 15 mmol L^{-1} hydroxypropyl-β-CD was used as mobile phase	Isocratic elution, 30 °C	[167]
Intact proteins, antibodies or peptides and their impurities	Biologics with a molecular weight ranging from 5.8 kDa to 150kDa	TSKgel G2000SWXL (7.8 mm × 30 cm, 5 μ) column, mobile phase containing 100 mM sodium acetate pH 6.0 and 100 mM Sodium sulfate with or without 1–10% hydroxypropyl-CD	Isocratic elution	[168]
Flavanone aglycones and 7-O-glycosides	Commercial Citrus juices	C18 capillary column, mobile phase consisting of 50 mM sodium acetate buffer pH 3 and 30% methanol containing 20 mM of carboxymethyl-β-CD or 10 mM of sulfobutyl ether-β-CD	Isocratic elution	[169]

abled separation of biologically relevant β-carboline alkaloids, namely norharmane, harmane and harmine in human serum. Prior to the work of Gonzalez-Ruiz et al., liquid chromatographic procedures for quantitation of β-carboline considered isocratic or gradient elution with high proportions of acetonitrile or methanol. In order to reduce the amount of organic solvent, pH of the aqueous phase should be lowered to 3.0, increasing the degradation of the stationary phase. Respectfully, these shortcomings were successfully overcome with an addition of CD to the mobile phase [6]. Chisvert et al. [173] demonstrated simultaneous determination of organic UV filters in sunscreen formulation, namely: benzophenone-4, benzophenone-3, butylmethoxydibenzoylmethane, octyl dimethyl PABA, octyl methoxycinnamate, homosalate and octyl salicylate. The developed method was labeled as eco-friendly since it used hydroxypropyl-β-CD in the mobile phase and ethanol as organic modifier. The isoflavone glycosides and aglycones present in Radix astragali samples have been separated using a methanol – water mobile phase containing (2-hydroxypropyl)-β-CD as mobile phase modifier in the paper published by Feng et al. [174]. Mobile phases including both micelles and CDs have been used in simultaneous determination of bisoprolol/hydrochlorothiazide and atenolol/chlorthalidone combinations in urine samples [175]. Zeng et al. [176] developed isocratic HPLC method employing CDs as mobile phase additives to differentiate among two species of Radix Puerariae and determine major isoflavonoids in the sample. Hydroxypropyl-β-CD appeared to be an important additive with a substantial power of reducing the retention of isoflavonoids, especially daidzein and genistein. Lv et al. investigated chromatographic behavior of four sesquiterpenoids in volatile oil of Curcumae Rhizoma on RP stationary phase methyl-β-CD as mobile phase additive [166]. Formation constants of inclusion complexes as well as enthalpy and entropy of binding were also determined. Study performed by Wang et al. showed that γ-CD has the ability to markedly reduce the retention of triterpenes (especially asiatic acid and madecassic acid), and improve the separation for madecassoside and asiaticoside B [170].

4.3.2. CD as mobile phase additive in chiral separations

Utilizing the host-guest complexation phenomenon, where a transient diastereomeric complex between CD and the guest molecule is formed, CDs are able to separate enantiomers. CDs represent most frequently used type of chiral selectors in chiral separations primarily in capillary electrophoresis (CE) based techniques, but also in chiral HPLC methods [177]. They possess numerous chiral centers, five in every glucose unit (for example β-CD has 35 different chiral recognition sites). Shapes of the glucose units do not repeat themselves from units to unit and because of that twisted shape, they own broader spectrum of enantio-recognition capacity than linear oligoglucosides [178]. Since they possess sufficient solubility in the mobile phases and low (negligible) UV absorbance in broadly used UV ranges for chromatographic detection and since most derivatives are cheap and affordable, there is no wonder why they are most commonly and prominent used as chiral mobile phase additives (CMPAs). Chemical modifications of native CDs by derivatization of hydroxyl groups are performed in order to increase solubility (especially in case of β-CD), so currently there is a large number of CDs' derivatives with neutral or ionic nature on the market. Modification could lead to changes in cavity's depth and/or flexibility, bringing new interaction sites, which results in variations of enantioselectivity [136, 179]. Except for use as CMPAs, CDs have a role in chiral separations using chiral stationary phases [180]. As this review is aimed at modification of LC mobile phase, the application of CDs as chiral stationary phases will not be further discussed.

Inclusion complex formation might be a key for enantio-recognition, but that is not always the case. Polar hydroxyl groups could play crucial role in the enantio-resolution process, through hydrogen bonding. Additionally, modification of hydroxyl groups could bring different interactions, affecting the formation of the inclusion complex between analytes and CD. More reactive reagents used for modification of CDs will react with hydroxyl groups at the narrower rim, but also with those on the wider rim, whereas, less reactive reagents will attack more selectively only the hydroxyl groups on narrower rim (6-hydroxy groups) [180].

The use of native CDs (α-, β- and γ-CD) as CMPAs in LC methods is widely represented in the literature [159, 181-183]. The most commonly used CD derivatives in chiral chromatography are derivatives of β-CD and those are hydroxypropyl-β-CD, sulphated β-CD, sulfobutylether-β-CD, methyl-β-CD [160-162, 164, 165, 167-169, 179, 183-192], but the following derivatives are also found, heptakis(2,3,6-tri-O-methyl)-β-CD, carboxymethyl-β-CD [163, 179].

As already mentioned, chiral recognition could be enhanced by derivatization of hydroxyl groups of native CDs, which has been utilized in plenty of papers [193]. Chen et al. reported the development of stereospecific HPLC for determination of sertraline in bulk drug, tablets and capsules. Addition of hydroxypropyl-β-CD to the mobile phase enabled the resolution of sertraline enantiomers and trans diastereoisomers [194]. Moreover, mixture of β-CD and hydroxypropyl-β-CD enabled the resolution of four sertraline enantiomeric forms in bulk drug [192]. Further, the structurally isomeric compounds of madecassoide were isolated by adding β-CD to the mobile phase on a C18 column [195]. Ye et al. reported enantioseparation of eight nonsteroidal anti-inflammatory drugs by using hydroxylpropyl-β-CD as chiral mobile phase additive in RP-HPLC. The developed method has an advantage over the methods with chiral stationary phase in terms of flexibility, easiness and economical aspect [186]. Utilizing hydroxypropyl-β-CD as chiral agent enabled the efficient separation of two structural isomeric pentacyclic triterpenes, oleanolic acid and ursolic acid [164] as well as mandelic acid, 4-methoxymandelic acid and 4-propoxymandelic acid [167]. Bao et al. investigated the retention behavior of two structural isomeric pentacyclic triterpenic acids, maslinic acid and corosolic acid by RP-HPLC with and addition of hydroxypropyl-β-CD [165]. Javeri et al. used hydroxypropyl-β-CD as mobile phase additive to enhance Size-Exclusion (SEC) HPLC resolution, and quantitation of aggregates in biologics by preventing its interactions with silanol groups of the commercial SEC–HPLC columns [168]. Addition of hydroxypropyl-β-CD or sulfobutylether-β-CD enabled enantioseparation of ten mandelic acid derivatives in RP-HPLC [196]. Results show that retention times of enantiomers and resolution are under the influence of pH, the organic modifier and the type of β-CD employed. Chiral mobile phases containing sulphated-β-CD were employed in separation of cathinones and amphetamines, in order to help in discovering whether the substances are sold as racemic mixtures [189]. The developed method successfully resolved enantiomers of amphetamine, while the method's applicability to resolve cathinone derivatives is limited. Further, Peng et al. published RP-HPLC method enabling enantiomeric separation of citalopram. The method uses sulfobutylether-β-CD as chiral mobile phase additive [191]. Zátopková et al. obtained chiral separation of eriocitrin, naringin, narirutin, and hesperidin diastereoisomers by adding sulfobutyl ether-β-CD to the mobile phase, while eriodictyol, naringenin, and hesperitin were resolved with an aid of carboxymethyl-β-CD [169].

Cyclodextrin complexation process is extremely temperature dependent. Therefore it is important to carefully choose optimal operating temperature. Zarzycki et al. examined inclusion complex formation at elevated (60 °C) and subambient (0 °C) temperature, using different CD types (native and their hydroxypropyl dervatives) as mobile phase additives on large set of achiral and chiral analytes (consisted of 7,8-dimethoxyflavone, steroids and polycyclic aromatic hydrocarbons). Enantiomers of acenaphthenol were successfully separated only using native CDs at subambient temperature (0 °C) [183].

5. Conclusion

The article shed some light on available strategies to modify mobile phases in LC systems. Chaotropic chromatography, MLC and β-CD-modified RP-HPLC are presented as solution to overcome various analytical challenges. Moreover, dealing with different analytical challenges

by only changing the mobile phase composition and using HPLC instruments is also beneficial, because it precludes the need for procurement of advanced analytical equipment. Moreover, MLC and β-CD-modified RP-HPLC contribute to the overall concept of sustainability in terms of separation of analytes more effectively in ecologically acceptable manner.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Nevena Djajić: Conceptualization, Methodology, Writing – original draft. **Jovana Krmar:** Methodology, Writing – original draft. **Milena Rmandić:** Writing – review & editing. **Marija Rašević:** Writing – review & editing. **Biljana Otašević:** Conceptualization, Supervision, Writing – review & editing. **Mira Zečević:** Supervision, Writing – review & editing. **Anđelija Malenović:** Conceptualization, Supervision, Writing – review & editing. **Ana Protić:** Conceptualization, Supervision, Resources, Writing – review & editing.

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