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Rania N. El-Shaheny*, Mahmoud H. El-Maghrabey, and Fathalla F. Belal

Micellar Liquid Chromatography from Green Analysis Perspective

Abstract: Micellar liquid chromatography (MLC) is a simple well-established branch of high-performance liquid chromatography. The applications of MLC for the determination of numerous compounds in pharmaceutical formulations, biological samples, food, and environmental samples have been growing very rapidly. MLC technique has several advantages over other techniques, such as simultaneous separation of charged and uncharged solutes, rapid gradient capability, direct on-column injection of physiological fluids, unique separation selectivity, high reproducibility, robustness, enhanced luminescence detection, low cost, and safety. This review is devoted to the evaluation of the agreement of MLC with the principles of green chemistry which recently represents a universal trend. Also, it provides an overview on the basics of MLC, in addition to a survey of MLC methods published in the past five years for the assay of various compounds in different matrices.

Keywords: micellar liquid chromatography, green analytical chemistry, pharmaceutical analysis, biological analysis

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1 Introduction

Micellar liquid chromatography (MLC) is one of the modes of reversed-phase liquid chromatography (RPLC) in which the mobile phases are aqueous solutions of a surfactant at a concentration above the critical micelle concentration (CMC). Over the past fifteen years, the popularity of MLC has grown rapidly. Micelles have also been used in many other separation techniques; such as electrokinetic chromatography [1,2], ultrafiltration, and cloud point extraction [3].

Although some publications have reported on the basics and applications of MLC for the analysis of drugs in pharmaceutical preparations and biological samples [4-11], the focus of this review is to highlight the importance of MLC for green analytical chemistry. Green chemistry has evolved from the pollution prevention approach developed within the USA's Environmental Protection Agency as a conceptual framework that minimizes the undesirable effects of chemistry. Many efforts have been made in the field of analytical chemistry to avoid the hazards of the analytical methodologies and to reduce the costs of analysis [12]. In this review article, we present a brief overview of the basics of MLC as well as a comprehensive discussion about its importance from green analytical chemistry perspective. In addition, details about the analytical applications of MLC in the past five years will be presented. It is our hope that this review will provide many fertile ideas to the readers.

2 Basics of micellar liquid chromatography

2.1 Critical micelle concentration and Krafft point

Surfactants are amphiphilic molecules that consist of a hydrophobic moiety and a polar head group. Above their CMC, surfactants form aggregates that are known as micelles. Micelles have a dynamic structure that is the result of the rapid exchange of surfactants in the aggregated and monomeric forms. The number of monomer surfactants in the aggregate form (called aggregation number) and the size of micelles vary greatly between surfactants. The CMC and aggregation number are the result of many factors, such as ionic strength, presence of a co-solvent and temperature. A suitable surfactant for MLC should have a low CMC. A high CMC would result in working at a high surfactant concentration, which would

***Corresponding author: Rania N. El-Shaheny:** Analytical Chemistry Department, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt, E-mail: rania_n2010@yahoo.com
Mahmoud H. El-Maghrabey, Fathalla F. Belal: Analytical Chemistry Department, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

create viscous solutions, giving undesirable high system pressure and background noise in UV detectors [5]. The selection is often limited to the following surfactants: the anionic sodium dodecyl sulphate (SDS), the cationic cetyltrimethylammonium bromide (CTAB), and the non-ionic polyoxyethylene 23 lauryl ether (Brij-35) whose main characteristics are summarized in Table 1.

Another property of ionic surfactants is the Krafft point, which is defined as the temperature at which the solubility of surfactant is equal to its CMC. Below the Krafft point temperature, the solubility of surfactant is quite low and the solution appears to contain no micelles. Chromatographic work in MLC should be conducted above this temperature to avoid surfactant precipitation. This means that the Krafft point should be well below room temperature [5].

Non-ionic surfactants also have a specific temperature, called the cloud point, above which phase separation occurs [5]. Chromatographic work with these surfactants should be conducted below this temperature (e.g. for aqueous 1–6% solutions of Brij-35, it is 100°C, whereas for Triton X–100 this value is 64°C).

2.2 Principles of separation by MLC

MLC shares the basic components of RPLC systems: a non-polar stationary phase and a polar aqueous mobile phase. However, hydro-organic mobile phases in conventional RPLC are homogeneous, whereas micellar solutions are heterogeneous, being consisted of two distinctive media: the amphiphilic micellar aggregates (micellar pseudophase) and the surrounding bulk water or aqueous-organic solvent that contains surfactant monomers in a concentration nearly equal to the CMC. On the other hand, the stationary phase is modified by the adsorption of surfactant monomers, creating a structure similar to an open micelle, and reducing silanophilic interactions. In micellar solutions, the concentration of monomer surfactants is essentially constant and equals the CMC. Thus, the composition of the stationary phase will not change with differences in the micelle concentration in the mobile phase. This is a different behavior than that found in RPLC, where the composition and conformation of the alkyl-bonded phase depend on the composition of the hydro-organic eluents [5,7].

Retention behavior in MLC is controlled by solute partitioning from the bulk solvent into micelles and into stationary phase as well as on direct transfer from the micelles in the mobile phase into the stationary phase. While retention of more polar compounds is determined by their partitioning from the bulk aqueous phase into micelle and alkyl stationary phase, the more hydrophobic compounds might be directly transferred from micelles in the mobile phase into the stationary phase [13,14].

The main drawback of MLC is the decreased column efficiency due to slow mass transfer from the stationary phase. Slow stationary phase mass transfer can be attributed to the poor "wetting" of the stationary phase with a purely aqueous mobile phase as well as to the adsorption of monomer surfactants that change the characteristics of the alkyl-bonded stationary phases [15]. To enhance the efficiency in MLC three main approaches have been adopted: addition of small concentrations of organic modifiers to the micellar mobile phase, increasing the column temperature, and decreasing the flow rate. For this reason, most procedures for the determination of compounds by MLC make use of micellar mobile phases containing an organic modifier, which is usually a short-chain alcohol (methanol, propanol, butanol or pentanol) or acetonitrile, so-called "hybrid micellar mobile phase". These modifiers increase the elution strength and often improve the shape of the chromatographic peaks. The modifiers act by solvation of the bonded stationary phase and decreasing the amount of surfactant adsorbed, such effect increases as the concentration and the hydrophobicity of the alcohol increases [15,16]. Meanwhile, the addition of triethylamine to a micellar mobile phase in combination with organic modifier enhances the efficiency over organic modifier added alone. This observation provides further evidence that efficiency and surfactant adsorption are linked by the effect of the latter on diffusion

Table 1: Characteristics of the most common surfactants in MLC[a]

Name	Molecular formula	Type	Molecular weight	CMC (mM)	Aggregation number at 25°C (monomer/micelle)	Krafft or cloud point (°C)
Sodium dodecyl sulfate (SDS)	$C_{12}H_{25}NaO_4S$	anionic	288	8.2	62	10
Cetyltrimethylammonium bromide (CTAB)	$C_{19}H_{42}BrN$	cationic	364	0.83	90	26
Polyoxyethylene 23 lauryl ether (Brij-35)	$C_{58}H_{11}8O_{24}$	non-ionic	1198	0.06	41	100

[a]Reference [5].

in the interfacial region between the mobile phase and stationary phase. Moreover, higher temperatures increase the kinetics of mass transfer. In general, operating under these conditions would enhance the column efficiency such that it becomes comparable with conventional RPLC. An interesting example is the case of basic compounds, which produce symmetrical peaks with high efficiencies in MLC, with columns that yield highly tailed peaks in RPLC without additives [16].

On considering the essential aspects of the analytical work, the analytical parameters emerge as the key factors to be considered. Accuracy, traceability, sensitivity, selectivity, and precision are the essential and basic goals which must be assured in order to provide to the industries, consumers, and strategy makers the appropriate tools to do their determinations. In the frame of analytical chemistry, MLC is an analytical technique that accomplishes the main analytical goals, in addition to the green parameters of the method as discussed below.

3 Green evaluation of MLC

In terms of ecological aspects, RPLC techniques are characterized by a large consumption of organic solvents. Developing a greener process in chromatography is a challenge. MLC constitutes a good alternative to RPLC which improves both economic and ecological aspects. MLC is greener than RPLC in all steps of the analysis from sample collection and preparation to separation and final determination. A discussion of the different points that contribute to the greenness of MLC is presented here:

3.1 Safety of reagents

Most MLC methods use hybrid mobile phases consisted of aqueous solutions of a surfactant above its CMC and a small portion of organic modifier (mostly 3–15%, v/v). As we stated earlier, SDS is the most commonly used surfactant in MLC, but CTAB and Brij-35 are also used. Micellar mobile phases are safer for both the operator and environment. Considering safety of the used surfactants, SDS is not carcinogenic when either applied directly to the skin or consumed [17]. A review of the scientific literature revealed that SDS was negative in an Ames (bacterial mutation) test, a gene mutation and sister chromatid exchange test in mammalian cells, and in an *in-vivo* micronucleus assay in mice. The negative results from *in-vitro* and *in-vivo* studies indicate that SDS does not interact with DNA. SDS has LD_{50} of 0.8–1.1 g kg^{1} in rats [17]. Based on the available data [18], CTAB is also considered safe. It is poorly absorbed from the intestine and is excreted in feces. It is absorbed into the skin, but not rapidly. Dermal exposure to 2% CTAB produced no evidence of teratogenicity. In addition, all mutagenesis tests and sensitization reactions were negative [18]. Fatty alcohol ethoxylate surfactants (e.g. Brij-35) were not found to cause genetic or reproductive damages. Also, no carcinogenic effects were noted in chronic studies either after oral or dermal exposure. Further, the fatty alcohol ethoxylates do not irritate the skin or eyes [19].

In comparison with the RPLC methods that employ aqueous–organic mobile phases, the micellar mobile phases have the advantage of using small amounts of organic modifier. Furthermore, propanol, butanol, and pentanol, the most common organic modifiers used in MLC, are retained in the micellar solution, thus reducing the risk of evaporation and making the micellar mobile phases more stable. In addition, they are also less toxic than methanol or acetonitrile, which are commonly used in conventional RPLC. The low content of organic solvents in the micellar mobile phases provides also the advantage of non-flammability and safety for laboratory work [9].

3.2 Waste generation

Since the possible contamination of the environment with wastes arising from analytical chemistry practice is an essential aspect for green chemistry, waste generation from MLC and its impacts should be discussed. Another important advantage of micellar mobile phases is the biodegradable character of surfactants used. SDS is a fatty alcohol sulfate that is aerobically degraded. Thomas and White [20] observed that 70% of ^{14}C SDS was degraded to CO_2 and the remaining 30% was incorporated into the microbial biomass, i.e., 100% of the SDS was utilized for either energy or biomass production. On the other hand, Brij-35 is one of the fatty alcohol ethoxylate derivatives, developed as an eco-friendly alternative to alkyl phenol ethoxylates [21]. A large number of reports have dealt with the biodegradability of these compounds. Linear fatty alcohol ethoxylate (e.g. Brij-35) are considered readily biodegradable. Kravetz *et al.* [22] observed 80% primary degradation in 28 days for such compounds. Meanwhile, CTAB belongs to the quaternary ammonium compounds which are also biodegradable through different pathways. One of these pathways is N-dealkylation, which involves monooxygenase activity with the production of trimethylamine and an alkyl residue [23,24]. Thus, waste generated from MLC could be considered a clean waste.

It is also worth noting that, mobile phase recycling is possible in case of MLC because of the low evaporation risk of organic solvents in hybrid micellar eluents. So, the micellar mobile phase can be recycled during the analysis, as long as a small number of injections are made.

On the other hand, due to the toxicity of methanol and acetonitrile, the most frequently used solvents in RPLC, safe disposal of the waste solvent is essential. Combustion in a hazardous waste plant, if available, is recommended. Otherwise, the waste can be degraded by chemical decomposition in laboratory through repetitive steps. Acetonitrile-water waste can be degraded to acetic acid and ammonia by treatment with excess sodium hydroxide. The waste must be diluted in water to 10% acetonitrile in order to prevent the formation of two-phase system upon addition of concentrated sodium hydroxide [25].

3.3 Sample treatment

3.3.1 Determination of drugs in pharmaceuticals

MLC offers important benefits compared to conventional RPLC concerning sample treatment. For example, it allows a drug solution to be injected into the chromatographic system without any treatment other than filtration, reducing the sample preparation time. Drugs are easily extracted when the samples are treated with micellar solutions, since the excipients are usually not soluble in the micelles. The presence of a small amount of alcohol into the micellar media can improve the solubility of the drugs [6]. The solubilizing ability of micelles is one of their most important properties that allows the analysis of complex matrices without the need for extraction, while providing direct injection of untreated samples. The sample preparation is very simple and varies according to the kind of pharmaceutical formulation, whether solid (tablets, capsules, pills, and powders), liquid (drops, solutions, suspensions, sprays, oily injection, and syrups), ointment, cream, gel, or suppository. For solid dosage forms, a suitable number of units are weighed, (carefully emptied in case of capsules) and pulverized. Then, suitable amounts of powdered dosage forms are weighed and dissolved in the micellar mobile phase. For liquids, pretreatment is simpler and includes mixing with a small amount of alcohol and dilution with the micellar mobile phase or dilution directly with the micellar mobile phase. For more complex dosage forms such as ointment, cream, or gel, a suitable amount is weighed and mixed with the micellar mobile phase with the aid of sonication, or mechanical stirring [6]. For suppositories, one unit is dissolved in n-propanol, butanol, or pentanol (according to the mobile phase composition) with the aid of sonication and gentle heating, and then suitable volumes are diluted with the mobile phase then chromatographed [26].

Following this sample preparation and the selection of a suitable micellar mobile phase, the recoveries usually agreed well with the contents declared by the manufacturers within the tolerance limits. Another advantage of MLC is the sample preparation time, which is shorter than that required in conventional RPLC procedures where long, tedious extraction steps are often needed. Hence, it decreases error sources due to the minimized risks of losses and chemical changes in the analyte because of the reduced number of steps. Thus, MLC offers the advantages of reduced cost and time of the analyses and increased sample throughputs.

3.3.2 Determination of drugs in biological fluids

A major drawback of conventional RPLC methods for the routine analysis of protein-based biological samples is the need for repetitive sample preparation steps, prior to injection, to remove proteinaceous materials. This is essential to prevent irreversible adsorption to the packing and column plugging by the background proteins. Protein precipitation is tedious and time-consuming, and can cause sample dilution or loss of material.

A fascinating feature of certain types of micelles, such as SDS and Brij-35, is their ability to solubilize proteins. This capability has been effectively exploited for the direct injection of untreated biological fluids onto RPLC columns. The micelles tend to bind proteins competitively by releasing protein-bound drugs, so the substances are free to partition into the stationary phase, whereas the proteins, rather than precipitating into the column, are solubilized and eluted with or shortly after the solvent front. Dilution of the biological samples with the micellar mobile phase and filtration of samples prior to injection helps to decrease the width of protein band appearing at the beginning of the chromatograms, thus preventing interferences with drug determination. Dilution of samples also helps to extend the life time of the column [27].

Possibility of direct injection of physiological samples with MLC precludes elaborate multiple extraction steps through traditional liquid-liquid extraction procedures, hence decreasing the time and costs of the analysis and avoiding the consumption of large quantities of flammable, toxic organic solvents. Direct injection with MLC is also more advantageous than solid-phase extraction technique which requires more time, multiple steps, and special

cartridges. Also, it is less complex than column-switching procedures, which require additional instrumentation (precolumns, switching valves, and additional pumps) and accurate timing of valve switching for a successful separation. Nevertheless, it is worth noting that cationic surfactants cause proteins to precipitate and cannot be usually used with physiological samples [27].

3.4 Compatibility with existing RPLC instruments

Another issue to be considered is the compatibility of MLC with existing RPLC instruments, since this matching would reduce the cost of MLC if there is no need for special instrumentations or resetting. Micellar mobile phases are compatible with RPLC stationary phases (C_{18}, C_8, cyanopropyl, phenyl, and monolith columns). In addition, gradient elution is also possible by increasing the concentration of micelles and/or organic modifier during the course of the separation [28,29]. However, the use of MLC would allow the simultaneous determination of hydrophobic and hydrophilic solutes in the same run with no need for gradient elution programs.

MLC is also well-matched with several RPLC detection modes such as ultraviolet, fluorescence, phosphorescence, chemiluminescence, electrochemical, diode array detection (DAD), and inductively-coupled plasma mass spectrometry. Interestingly, micellar mobile phases could sometimes lead to improvements in the detection capabilities. The fluorescence intensity of certain compounds in micellar media can be dramatically increased due to micellar solubilization [5,30-32]. Solutes that are localized in the anisotropic media of micelles experience a microenvironment with different polarity and higher viscosity than those of the bulk aqueous solvent. As a result, their freedom of movement is limited in the micelles and results in the shielding of compounds from non-radiation deactivation and/or an increase in quantum efficiency. Consequently, fluorescence signals are often intensified in the presence of micelles. Even room temperature liquid phosphorescence has been observed in ionic micellar solution with heavy atom counter-ions, which is attributed to the micelle stabilization effect of the triplet state of some molecules [5,32]. Moreover, the hydro-organic mobile phases used in conventional RPLC are detrimental to inductively-coupled plasma mass spectrometry analytical performance. Hydro-organic mobile phases may decrease sensitivity due to excessive solvent loading of the plasma, plasma instability, high background (due to the formation of molecular ions), and carbon deposition on the sampling cone. Using micellar mobile phases with this detection mode is therefore worthwhile [5]. Hence, we conclude that MLC does not require any modification of existing instrumentation; rather, it even has advantages such as lower detection limits.

4 Applications of MLC

The popularity of the applications of MLC in the determination of various compounds in pharmaceutical products, biological fluids, food samples, and environmental samples has grown rapidly in recent years. Many MLC methods were published in the past five years for the determination of various compounds in different matrices mostly using hybrid micellar mobile phases consisted of aqueous surfactant solution and small volume of organic modifiers. A survey of the MLC methods published in the past five years (2010 through early 2015) is presented in Table 2.

Many MLC methods have been reported for the determination of a wide range of compounds in different pharmaceutical preparations and pure drug substances [33-48]. Although most of these methods used hybrid mobile phases containing SDS as a surfactant, some of them also used Brij-35 [33,37,42] and Tween-20 [35,40,46,48]. Among such methods, Memon *et al.* [37] studied the non-ionic surfactant Brij-35 for its selectivity in the separation of positional isomers. The non-ionic surfactant interacts differently than ionic surfactants. The study showed dipolarizability, excess molar refraction and basicity. Such parameters are responsible for separation in the case of non-ionic MLC.

Additionally, some stability-indicating MLC methods were developed to study the degradation behavior of some pharmaceutical compounds including flavoxate HCl [36], nelfinavir mesylate [40], risedronate [43], and timolol maleate [47]. Recently, El-Shaheny developed a stability-indicating MLC method for piroxicam, tenoxicam, and lornoxicam [41]. This method was also applied for the determination of these compounds in complex matrix formulations, including suppositories and gel by direct injection of samples without pretreatment steps other than dilution and filtration.

One of the main applications of MLC is the possibility of direct sample injection of biological materials onto the column due to the ability of micellar aggregates to dissolve sample proteins and other compounds. Many methods have been reported for the determination of several compounds in biological fluids such as plasma, serum, urine, gastric fluid, and intestinal fluid [49-80]. Almost all

Table 2: Recent applications of MLC in different matrices

Compound	Matrix	Chromatographic conditions	Column	Detection	Ref.
I. Pharmaceutical preparations and pure drugs					
amitriptyline, clomipramine, doxepin, imipramine, maprotiline, nortryptiline, and trimipramine	tablets and capsules	0.02 M Brij-35 at pH 3 adjusted with 0.01 M citric acid monohydrate, at 1 mL min^{-1}, 25°C	C_{18}	UV detection at 254 nm	33
atenolol and hydrochlorothiazide	tablets	0.07 M SDS at pH 3 adjusted with phosphate buffer-15% (v/v) *n*-propanol, at 1.5 mL min^{-1}	C_{18}	UV detection at 225 nm	34
atorvastatin calcium and pioglitazone	tablet	Tween-20-*n*-butanol-phosphate buffer (pH 4.2) (50:25:25 v/v/v), at 1.5 ml min^{-1}, 25°C	C_{18}	UV detection at 322 nm	35
flavoxate HCl	tablets	0.15 M SDS-15% *n*-propanol-0.3% triethylamine-0.02 M orthophosphoric acid, pH 2.5, at 1 mL min^{-1}	phenyl	UV detection at 325 nm	36
isomers of parabens, nitroanilines, nitrophenols, and quinolinols	pure drug substance	gradient elution with Brij-35-*n*-propanol in various percentages	Chromolith C_{18}	UV detection	37
metformin, nateglinide, and gliclazide	tablets	0.12 M SDS-10% *n*-propranol-0.3% triethylanine, pH 5.6 using orthophosphoric acid, at 1 mL min^{-1}	C_{18}	UV detection at 254 nm	38
morphine, codeine, papaverine, and noscapine	solution for injection	0.1 M SDS-5% *n*-butanol, pH 2.5 by phosphoric acid, at 1 mL min^{-1}, 40°C	C_{18}	UV detection at 280 nm	39
nelfinavir mesylate	tablets	0.5 M Tween-20-2% *n*-butanol, at 1.5 mL min^{-1}, 25°C	C_{18}	UV detection at 249 nm	40
piroxicam, tenoxicam, lornoxicam, and their degradation product (2-aminopyridine)	tablets, capsules, vials, gel, and suppositories	0.15 M SDS-10% *n*-propanol-0.3% triethylamine-0.02 M orthophosphoric acid (pH 3 or 6), at 1 mL min^{-1}	C_8	programmed UV detection	41
pseudoephedrine, paracetamol, and chlorpheniramine	cold compound preparations	(aqueous solution containing 3.0×10^{-3} M Brij-35 and 2.0×10^{-2} M potassium dihydrogen phosphate)-methanol (96:4, v/v) at pH 3	C_{18}	programmed UV detection	42
risedronate	tablets	0.02 M SDS-0.3% triethylamine-10% *n*-propanol-0.02 M orthophosphoric acid, at 0.7 mL min^{-1}	C_{18}	UV detection at 262 nm	43
sildenafil citrate	oral suspensions and tablets	8.2 mM SDS in acetate buffer (pH 4), at 0.5 mL min^{-1}	C_{18}	UV detection at 298 nm	44
tamoxifen	tablets	0.15 M SDS-7% *n*-pentanol (pH 3), at 1.5 mL min^{-1}, 40°C	C_{18}	fluorescence detection at 260/380 nm	45
2,4,5,6-tetraamino pyrimidine sulfate	pure drug substance	5% *n*-butanol in 0.05 M Tween-20	C_{18}	UV detection at 215 nm	46
timolol maleate in the presence of its degradation products	eye drops	0.1 M SDS-10% *n*-propanol-0.1% triethylamine-0.035 M orthophosphoric acid, at 0.1 mL min^{-1}	phenyl	UV detection at 298 nm	47

Continued **Table 2:** Recent applications of MLC in different matrices

Compound	Matrix	Chromatographic conditions	Column	Detection	Ref.
torsemide and spironolactone	tablet	Tween-20-*n*-butanol-phosphate buffer (50:25:25 v/v/v) adjusted to pH 3.5, at 1.5 mL min^{-1}, 30°C	C_{18}	UV detection at 261 nm	48
II. Biological fluids					
abacavir, lamivudine, and raltegravir	plasma	0.05 M SDS at pH 7, at 1 mL min^{-1}	C_{18}	UV detection at 260 nm	49
acebutolol, atenolol, carteolol, labetolol, metoprolol, and propranolol	urine	gradient elution with mobile phase containing fixed concentration of SDS (0.1 M) and the *n*-propanol content was linearly increased from 0 to 30%, 25°C	C_8	UV detection at 225 nm	50
benzodiazepines	serum	0.13 M SDS-2.4% *n*-pentanol-0.01 M phosphate buffer-0.1% triethylamine (pH 7), at 1 mL min^{-1}, 25°C	C_8	UV detection at 240 nm	51
buspirone hydrochloride	plasma	1.0 mM of Brij-35 in phosphate buffer (0.02 M, pH 6), 1 µL min^{-1}	diphenyl capillary column	on-chip microfluidic chemiluminescence detection	52
carbaryl and 1-naphthol	urine and serum	0.15 M SDS–6% *n*-pentanol-0.01 M NaH_2PO_4 buffered at pH 3, at 1 mL min^{-1}	C_{18}	fluorescence detection at 225/333 nm	53
citalopram, paroxetine, and fluoxetine	plasma and urine	0.075 M SDS-6% *n*-butanol buffered at pH 7, at 1 mL min^{-1}, 25°C	C_{18}	programmed fluorescence detection	54
danuravir, ritonavir, emtricitabine, and tenofovir	plasma	0.06 M SDS-2.5% *n*-pentanol (pH 7), at 1 mL min^{-1}	C_{18}	UV detection at 214 nm	55
diltiazem hydrochloride, metoprolol tartrate, and isosorbide mononitrate	serum	0.0415 M SDS-0.02 M sodium dihydrogen phosphate-10% *n*-propanol (pH 7.0), at 0.8 mL min^{-1}, 40°C	cyano	DAD at 225 nm	56
disopyramide, lidocaine, and quinidine	serum	150 mM SDS-7% *n*-butanol-10 mM phosphate buffer pH 7-0.9% (w/v) NaCl, at 1 mL min^{-1}, 25°C	C18	UV detection at 214 nm	57
felodipine	plasma and tablets	85 mM SDS-25 mM phosphate buffer-6.5% *n*-pentanol at pH 7, at 1.5 mL min^{-1}, 30°C	C_{18}	fluorescence detection at 240 nm/440 nm	58
floctafenine and its metabolite and hydrolytic degradation product (floctafenic acid)	plasma and tablets	0.15 M SDS-10% *n*-propanol-0.3% triethylamine in 0.02 M orthophosphoric acid (pH 3), at 1 mL min^{-1}	C_8	UV detection at 360 nm	59
furosemide, metoprolol, and verapamil	human plasma	0.15 M SDS-25 mM Na_2HPO_4)-*n*-butanol-triethylamine (93:6:1, v/v/v), pH 3 using H_3PO_4, at 2 mL min^{-1}, 40°C	C_{18}	UV and fluorescence detection	60
itraconazole	plasma and capsule	0.1 M SDS-20% *n*-propanol-0.3% triethylamine -0.02 M orthophosphoric acid (pH 3.5), at 2 mL min^{-1}	cyano	UV detection at 258 nm	61
lamivudine and its carbonate derivatives	simulated gastric and intestinal fluids	0.15M SDS-4% *n*-butanol-0.01 M KH_2PO_4-Na_2HPO_4 (pH 7), at 1 mL min^{-1}, 30°C	C_{18}	UV detection at 272 nm	62

Continued **Table 2:** Recent applications of MLC in different matrices

Compound	Matrix	Chromatographic conditions	Column	Detection	Ref.
melamine	plasma and urine	0.2 M SDS buffered at pH 3, at 1 mL min^{-1}	C_{18}	UV detection at 210 nm	63
nicotine	serum, tobacco, and dermal patch	0.15 M SDS-6% *n*-pentanol-0.01 M NaH_2PO_4 (pH 6)-0.001 M KCl, at 1 mL min^{-1}	C_{18}	electrochemical detection at 0.8 V	64
norfloxacin and tinidazole	human plasma and pharmaceutical dosage forms	0.15 M SDS, 0.3 % triethylamine, 5% *n*-propanol, pH 4 with 0.02 M orthophosphoric acid, at 1 mL min^{-1}	C_{18}	UV detection at 275 nm	65
paroxetine	blood and urine	0.15 M SDS-6% *n*-pentanol (pH 3), at 1 mL min^{-1}	C_{18}	electrochemical detection at 0.8 V	66
penicillin antibiotics	urine, tablets and enteric-coated capsules	0.11 M SDS-6% *n*-propanol-0.01 M NaH_2PO_4 buffered at pH 3, at 1 mL min^{-1}	C_{18}	UV detection at 210 nm	67
positron emission tomography radio ligand	human plasma	1% Triton X-100-100 mM SDS-8% *n*-butanol in 200 mM ammonium phosphate, pH 7, at 5 mL min^{-1}	monolithic C_{18}	UV detector in series with a dual bismuth germanium oxide coincidence radiation detector	68
positron emission tomography radio ligand	human and monkey plasma	gradient elution with acetonitrile-50 mM SDS in 10 mM ammonium phosphate (pH 7), at 10 mL min^{-1}	monolithic semi-preparative C_{18}	UV detector in series with a dual bismuth germanium oxide coincidence radiation detector	69
positron emission tomography radio ligand	human and monkey plasma	gradient elution with100 mM SDS-*n*-butanol in 10 mM sodium phosphate (pH 7.2), 5 mL min^{-1},	semi-preparative C_{18}	UV detector in series with a dual bismuth germanium oxide coincidence radiation detector	70
positron emission tomography radio ligand	human and monkey plasma	1-2% Triton X-100, 100 mM SDS, 0–5% *n*-butanol in 200 mM ammonium phosphate at pH 7, at 8.0 mL min^{-1}	monolithic semi-preparative C_{18}	UV detector in series with a dual bismuth germanium oxide coincidence radiation detector	71
ribavirin, silybin, interferon alpha 2a, lamivudine, and ursodeoxycholic acid	human plasma and tablets	0.1 M SDS-8% *n*-propanol-0.3% triethylamine-0.02 M phosphoric acid (pH 6), at 0.8 mL min^{-1}	C_{18}	UV detection at 214 nm	72
sertaconazole and terconazole	spiked human plasma, solution, powder, and suppository	0.1 M SDS-20% *n*-propanol- 0.3% triethylamine-0.02 M ortho-phosphoric acid (pH 4), at 1 mL min^{-1}	cyano	UV detection at 225 nm	73
tamoxifen and its main metabolites	plasma samples from breast cancer patients	0.08 M SDS-4.5% *n*-butanol (pH 3) at 1.5 mL min^{-1}, 40°C	C_{18}	fluorescence detection at 260/380 nm	74
tamoxifen and endoxifen	plasma samples from breast cancer patients	0.15 SDS-7% *n*-butanol (pH 3), at 1.5 mL min^{-1}, 40°C	C_{18}	fluorescence detection at 260/380 nm	75
tamoxifen	plasma samples from breast cancer patients	0.15 M SDS-7% *n*-butanol (pH 3), at 1.5 mL min^{-1}, 40°C	C_{18}	fluorescence detection at 260/380 nm	76

Continued **Table 2:** Recent applications of MLC in different matrices

Compound	Matrix	Chromatographic conditions	Column	Detection	Ref.
tinidazole, ciprofloxacin, and norfloxacin	spiked human plasma and pharmaceutical dosage forms	0.1 M SDS, 20% *n*-propanol, 0.3% triethylamine in 0.02 M orthophosphoric acid:water (60:40, v/v) (pH 4), at 1 mL min^{-1}	cyano	UV detection at 258 nm	77
tizoxanide	urine and plasma	0.1M SDS-8% *n*-propanol-0.3% triethyamine-0.02 M phosphate buffer (pH4), at 1 mL min^{-1}	monolithic C_{18}	UV detection at 240 nm	78
zidovudine derivatives	aqueous, simulated gastric and intestinal fluids matrices	0.05 M SDS-1% (v/v) *n*-butanol-0.01 M NaH_2PO_4 (pH 3), at 1 mL min^{-1}, 30°C	C_{18}	UV detection at 267 nm	79
zopiclone and its degradation product (2-amino-5-chloropyridine)	urine and tablets	0.15 M SDS-10% *n*-propanol-0.3% triethylamine-0.02 M orthophosphoric acid (pH 3.5), at 1 mL min^{-1}	phenyl	time programmed fluorescence detection	80
III. Food samples					
ampicillin and amoxicillin	chicken muscles, chicken liver, bovine muscles, liver, kidney, and eggs	0.05 M SDS-5% *n*-propanol-0.3% triethylamine in 0.02 M phosphoric acid buffered at pH 5, at 1 mL min^{-1}	C_{18}	UV detection at 220 nm	81
carbadox and olaquindox	chicken muscles, chicken liver, bovine meat, liver and milk, baby formulae	0.1M SDS-0.3% triethylamine-10% *n*-propanol in 0.02M phosphate buffer pH 4, at 1 mL min^{-1}	C_{18}	UV detection at 373 nm	82
ethopabate	chicken muscles, liver, eggs, and baby food	0.1M SDS-10% *n*-propanol-0.3% triethylamine-phopsphate buffer pH 4, at 1 mL min^{-1}	C_{18}	fluorescence detection at 271/364 nm	83
flunixin meglumine	bovine liver and kidney and pharmaceutical dosage forms	0.15 M SDS-8% *n*-butanol- 0.3% triethylamine in 0.02 M phosphoric acid buffered at pH 7, at 1 mL min^{-1}	C_{18}	UV detection at 284 nm	84
hydroxytyrosol	olive extract samples	0.05 M SDS-4% methanol buffered at pH 7, at 1 mL min^{-1}	C_{18}	UV detection at 280 nm	85
lidocaine, ketamine, and diazepam	foodstuffs	0.15 M SDS-6% *n*-pentanol (pH 7)	C_{18}	UV detection at 230 nm	86
melamine	milk	0.05M SDS-7.5% *n*-propanol, buffered at pH 3, at 1 mL min^{-1}	C_{18}	UV detection at 210 nm	87
melamine	dietetic supplements	SDS buffered at pH 3	C_{18}	UV detection	88
melamine	swine kidney	0.11 M SDS-7.5 % *n*-propanol at pH 3, at 1 mL min^{-1}	C_{18}	UV detection at 210 nm	89
oxytetracycline, tetracycline, chlorotetracycline, and doxycycline	foodstuffs	0.03 M SDS-7% *n*-butanol-0.02 M oxalic acid/NaOH, pH 2.5, at 0.8 mL min^{-1}	C_{18}	programmed UV detection	90
putrescine and tyramine	fish sauce	0.15 M SDS-6% *n*-butanol, pH 7, at 1 mL min^{-1}	C_{18}	UV detection at 260 nm after derivatization with 3,5-dinitrobenzoyl chloride	91

Continued **Table 2:** Recent applications of MLC in different matrices

Compound	Matrix	Chromatographic conditions	Column	Detection	Ref.
quercetin, hesperetin, and chrysin	honey	0.124 M SDS- 7.8% ethanol-5.0% v/v acetic acid, at 1 mL min^{-1}	C_{18}	UV detection at 269nm	92
quinolones	milk and eggs	0.05 M SDS-10% *n*-butanol-0.5% (v/v) triethylamine buffered at pH 3, at 1 mL min^{-1}, 25°C	C_{18}	programmed fluorescence detection	93
spermine	fish sauce	0.15 M SDS-4% *n*-pentanol at pH 7, at 1 mL min^{-1}, 25°C	C_{18}	UV detection at 260 nm after derivatization with 3,5-dinitrobenzoyl chloride	94
tylosin and josamycin residues	chicken muscles, chicken liver, bovine muscles, liver, milk, eggs, chicken-based baby food and baby formulae	0.17 M SDS-14% methanol-0.3% triethylamine-0.02 M phosphoric acid buffered at pH 4, at 2 mL min^{-1}	C_{18} monolithic	time-programmed UV detection	95
IV. Environmental samples					
benzidine, 1-amino-2-methylbenzene, and 2-methoxy-5-methylaniline	waste water	0.085 M SDS-3.2% (*n*-pentanol buffered at pH 7, at 1 mL min^{-1}	C_{18}	UV detection at 280 nm	96
blasticidin S and kasugamycin	irrigation water	69.3 mM SDS-water (50:1, v/v), at 1 mL min^{-1}	C_{18}	DAD at 210 nm	97
carbaryl and 1-naphthol	water, soil, and vegetables	0.15 M SDS-6% *n*-pentanol-0.01 M NaH_2PO_4 buffered at pH 3, at 1 mL min^{-1}	C_{18}	fluorescence detection at 225/333 nm	98
melamine	drinking water and wastewater	0.1 M SDS-7.5% *n*-propanol buffered at pH 3	C_{18}	UV detection at 210 nm	99
V. Herbal and plant extracts					
arbutin and hydroquinone	medicinal plant extracts and commercial cosmetic products	1% acetonitrile-0.006 M Brij-35 (pH 6), at 1 mL min^{-1}	C_{18}	UV detection at 280 nm	100
disulfiram	herbal extract, divine ash, traditional medicine, pharmaceutical, and urine	0.1 M SDS-*n*-butanol 4% (v/v) buffered to pH 7, at 1 mL min^{-1}	C_8	DAD at 248 nm	101
ephedrine, pseudoephedrine, and methylephedrine	ephedra herb and traditional Chinese medicinal preparations	0.175 M SDS-0.02 M potassium hydrogen phosphate-10% (v/v) methanol, pH 3, at 1.5 mL min^{-1}, 40°C	C_{18}	UV detection at 210 nm	102
strychnine and brucine	herbal preparations, homeopathic medicines, seeds of Nux-vomica, spiked serum, real urine samples	0.1 M SDS-4% *n*-pentanol NaH_2PO_4 buffered at pH 3, at 1 mL min^{-1}, 25°C	C_{18}	UV detection at 258 nm	103

of these methods used hybrid mobile phases containing SDS and organic modifier. On the other hand, two reports employed mixed micellar mobile phases containing SDS and Triton X-100 [68,71]. Only one method employed a micellar mobile phase containing Brij-35 together with acetonitrile as an organic modifier, a capillary column, and a microfluidic-based chemiluminescence detector for the direct analysis of buspirone in human plasma [52].

Raviolo and colleagues studied the stability of three new anti-HIV agents, which were obtained by the association of zidovudine with different amino acids, in different matrices including simulated gastric fluid and simulated intestinal fluid using MLC procedure [79]. Gualdesi *et al.* also developed an MLC method to study the stability of lamivudine and seven carbonate analogues in simulated gastric and intestinal fluids [62]. Such an approach represents an important addition to the applications of MLC.

Recently, MLC emerged as a promising separation technique for plasma metabolite analyses of short-lived radioligands, due to its potential to simplify and minimize sample processing time. This would in turn lead to less radioactive decay of the radionuclides and thus provide more accurate and precise determination. Nakao and team developed pioneering work in this field using MLC for the analysis of positron emission tomography radioligands and their radioactive metabolites in the plasma of humans and of monkeys [68-71].

Another interesting application of MLC is the analysis of food samples [81-95]. This includes the determination of several compounds in chicken muscles and liver [81-83,95]; bovine meat, liver, and kidney [81,82,84,95]; swine kidney [89]; eggs [81,83,93,95]; milk [82,87,93,95]; baby food [82,83,95]; honey [92]; fish sauce [91,94]; feeding staff [86,90]; olive extract samples [85]; and dietetic supplements [88]. MLC has been shown to be a very efficient technique for food analysis, avoiding long and tedious extractions of such complex matrices while providing high percentage recoveries with high accuracy and precision.

Moreover, MLC has been used for the determination of harmful and dangerous compounds in environmental samples. Some banned toxic aromatic amines, namely benzidine, 1-amino-2-methylbenzene, and 2-methoxy-5-methylaniline, were identified in waste water by MLC method [96]. In addition, the antibiotic fungicides blasticidin S and kasugamycin were found in irrigation water using MLC [97]. Also, the synthetic insecticide carbaryl and its main metabolite 1-naphthol were identified in water, soil, and vegetables (lettuce) by MLC [98]. Beltrán-Martinavarro *et al.* have developed a MLC method for the detection of the synthetic chemical melamine in drinking water and wastewater [99].

Another important application of MLC is the detection of naturally occurring phytochemicals in herbal and plant extracts [100-103]. An MLC method was applied for the analysis of the skin whitening agent arbutin and hydroquinone in pear fruits as well as in creams [100]. Determination of disulfiram in illicit preparations (ayurvedic, herbal, divine ash, and traditional medicine), as well as in pharmaceuticals and urine has also been accomplished by an MLC method [101]. Ephedrine, pseudoephedrine, and methylephedrine have also been identified in Ephedra herb and in two traditional Chinese preparations adopting an MLC method [102]. Strychnine and brucine were also identified by an MLC method in several matrices: herbal preparations, homeopathic medicines, seeds of Nux-vomica, spiked serum, and real urine samples [103].

Finally, looking at an overview of the published papers on MLC in the 2010-early 2015 time period yields some useful statistical information. Fig. 1a illustrates the frequency of the different fields of applications of MLC in this period. The most frequent application of such technique is the analysis of biological fluids, which represents 31% of the total publications in this time period, with an additional 14% applied in the analysis of biological fluids as well as pharmaceutical preparations. This widespread application of MLC in the field of bioanalysis is attributed to possibility of direct sample injection with no need for any pretreatment other than filtration.

Surveying the scientific literature published on MLC in this time period also revealed that SDS is the most frequently used surfactant, being used in 84% of the published work. Brij-35 and Tween-20 were also used but to a much lesser extent (7 and 6%, respectively), with a few workers used mixed micelles of SDS and Triton X-100 (3%). Fig. 1b shows the frequency of use of these surfactants in this time period. The popularity of using SDS is due to its availability in high purity, relatively low cost, and efficiency in dissolving biological fluids (which is not possible for cationic surfactants). Moreover, SDS is also selected because the dynamic of its micelles is better known than that of other micellar systems [5].

In conclusion, the increasing number of published MLC methods reflects the tendency of the analytical chemistry community toward green methods, which improve safety to the analysts and the environment. We hope that bringing this comprehensive review of such a fascinating technique illuminates its importance as a green separation method and becomes a factor in its further dissemination in various fields of application.

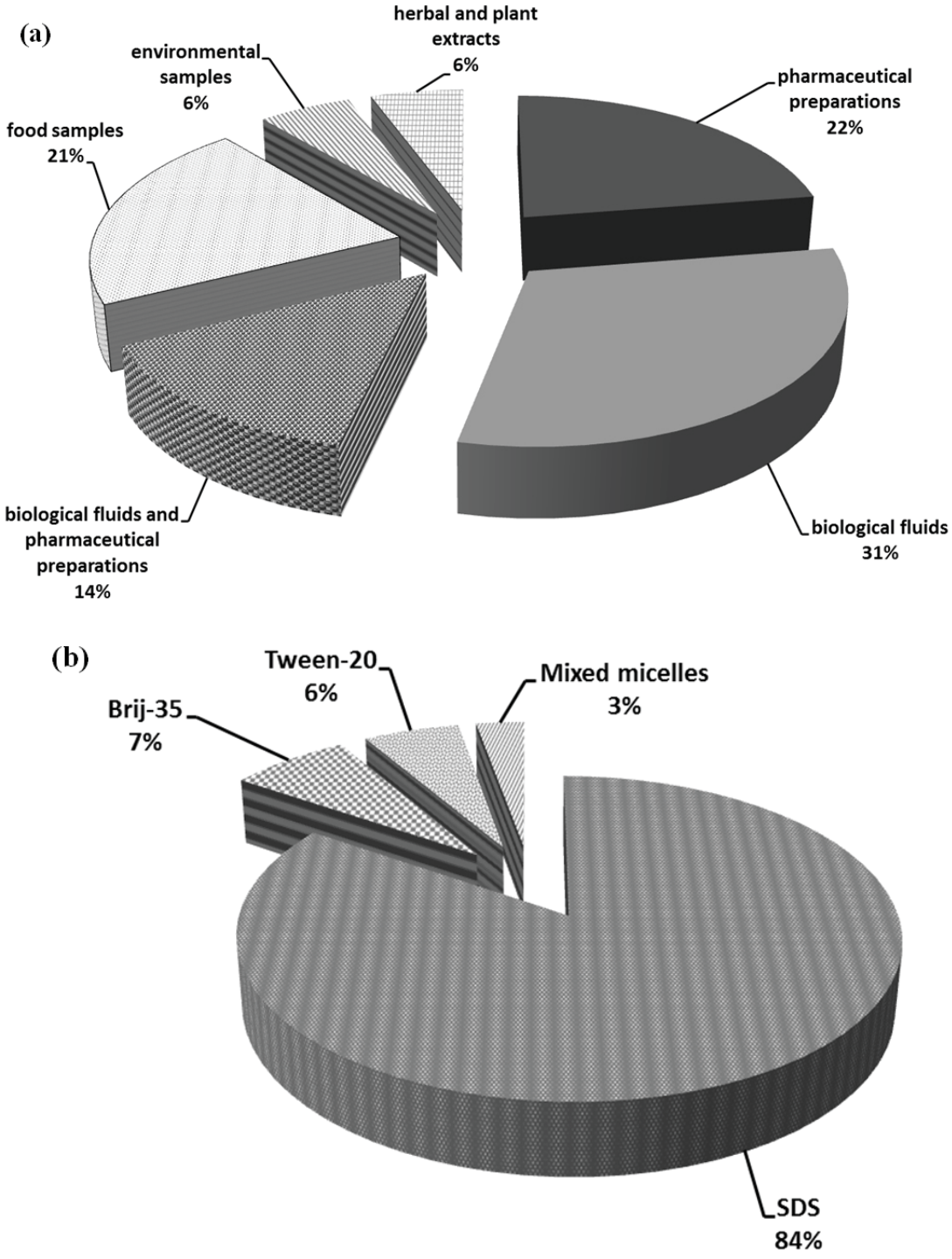

Figure 1: Frequency of (a) MLC applications in different fields and (b) using of different surfactants in MLC procedures, in the time period of 2010-early 2015.

5 Conclusion

Micellar Liquid Chromatography is a powerful separation technique that has been applied to different pharmaceutical, biomedical, and environmental studies of single and complex compounds. MLC analysis meets the requirements of green chemistry conception by using environment-friendly reagents; micellar mobile phases are less toxic, are non-flammable, and have lower environmental impact compared to conventional RPLC

methods. Micellar mobile phases are also less expensive than hydro-organic mobile phases, they allow the direct determination of physiological samples without pretreatment steps, and they are well-matched with ordinary RPLC instrumentation, so they do not require special preparations. It is evident that many principles of green chemistry are already established in MLC which will improve safety to the operator and the environment.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Abbreviations

Brij-35	polyoxyethylene 23 lauryl ether
CMC	critical micelle concentration
CTAB	cetyltrimethylammonium bromide
DAD	diode array detection
MLC	micellar liquid chromatography
RPLC	reversed-phase liquid chromatography
SDS	sodium dodecyl sulphate

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