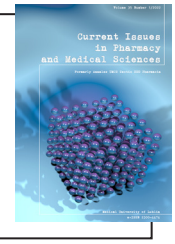
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Determination of some drugs used against neurodegenerative disorders by micellar electrokinetic chromatography with running buffer containing SDS

Adam Traczuk, Kamila Jaglinska, Beata Polak*

Department of Physical Chemistry, Medical University of Lublin, Poland

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ABSTRACT

In this work, analysis of some drugs used in the treatment of neurodegenerative disorders (sulpiride, olanzapine, carbamazepine, trazodone, clomipramine, and pridinol) was achieved through micellar electrokinetic chromatography (MEKC). The effect of surfactant (sodium dodecylsulphate), acetonitrile, and buffer pH and concentration on the solute retention was also investigated. Successful separation of all compound mixtures was obtained. The method was applied for the quantitative analysis of investigated compounds, and the LOD and LOQ were determined. The LOD values were in the range from 0.0127 mg/mL for clomipramine, to 0.1398 mg/mL for pridinol, while LOQ were in the range 0.0384 mg/mL for clomipramine, to 0.4237 for pridinol. The mode was also applied for the determination of investigated solutes in pharmaceutical prescriptions.

INTRODUCTION

Biogenic amines such as acetylcholine, dopamine, noradrenaline and serotonin play a vital role in the human body by acting as neurotransmitters – converting electrical signals at axon terminals into chemical signals within special receptors. However, problems with signal transitions result in many severe disorders. Therefore, drugs that block or inhibit their re-uptake within the above-mentioned receptors are used in handling nervous system diseases (e.g., depression, Parkinson's disease, epilepsy). Still, many patients are dealing with more than one neurodegenerative disorder at the same time.

Consequently, the treatment includes the co-administration of various classes of drugs. Thus, an antagonist at the D2 and D3 dopaminergic receptors (e.g., sulpiride) is mixed with an antagonist at the D4 dopaminergic (muscarinic M), and serotonergic 5HT2A receptors (e.g., olanzapine), or with 5HT2C serotonergic antagonists (trazodone and clomipramine), muscarinic receptor blocking and myorelaxant (e.g., pridinol), glutamate receptor blocking (e.g., carbamazepine).

As for sulpiride and olanzapine, their main use is in treating schizophrenia, doing so by blocking dopaminergic receptors according to the dopaminergic theory of schizophrenia. The latter indicates the emergence of positive (productive) symptoms of overactivity in the mesolimbic dopaminergic pathway. On the other hand, a decrease in dopaminergic activity in mesocortical dopaminergic projections may cause negative symptoms [1]. In contrast, 5HT2C serotonergic antagonists are used as antidepressants. Moreover, like all cholinolytics, pridinol blocks muscarinic receptors and has been found useful in treating Parkinson's disease, while carbamazepine is employed to mitigate the effects of epilepsy, bipolar disorder, depression and schizophrenia [2,3]. Neurodegenerative disorders are a global problem and demonstrate an almost 40% death rate during the last 30 years [4].

The above-mentioned fact indicate that the analysis of these drugs by various separation techniques is necessary. So, to label these drugs, high-performance liquid chromatography (HPLC) [5,6], and micellar electrokinetic chromatography (MEKC) [7], were applied. Moreover, some drugs, e.g., clomipramine, were investigated using biopartitioning micellar chromatography (BMC) [8]. In addition, gas chromatography [9], HPLC with electrochemical [10] and UV detection [11], as well as capillary electrophoresis (CE) [12,13] were used to separate tricyclic antidepressants.

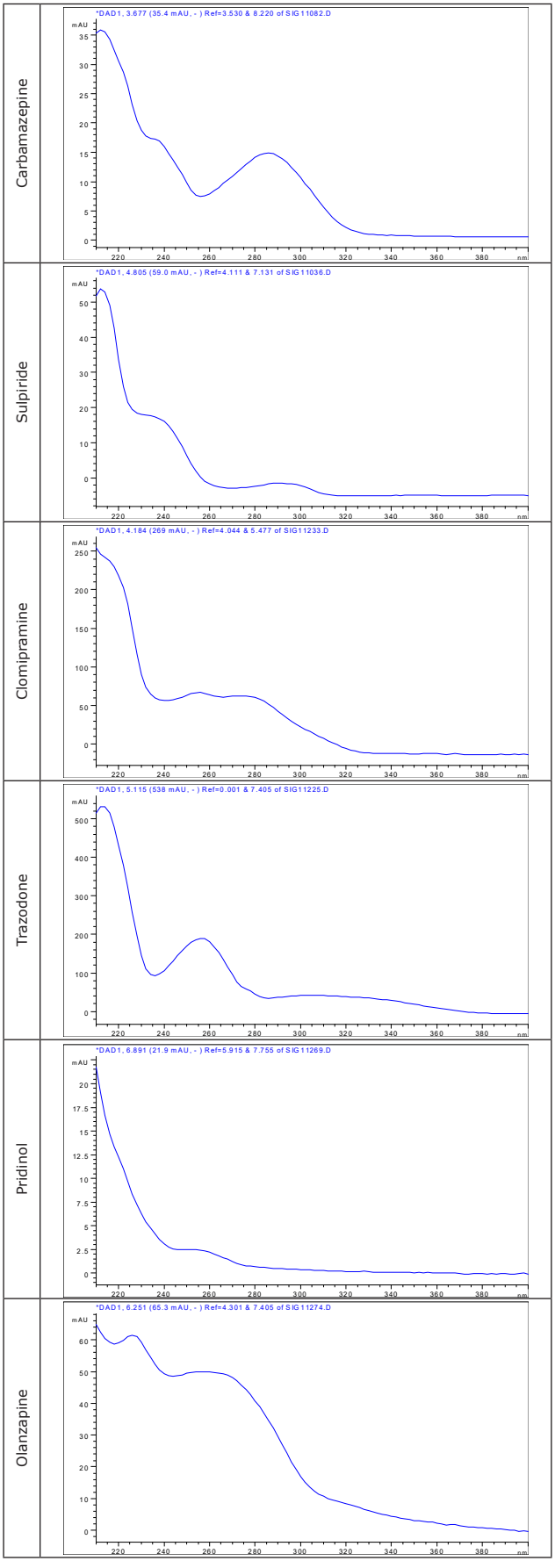
The main goal of our work was to find the most suitable running buffer conditions for effective application of the micellar electrokinetic chromatography (MEKC), technique that will allow the separation of a mixture containing various classes of drugs (sulpiride, olanzapine, clomipramine, trazodone, pridinol, and carbamazepine) applied against neurodegenerative disorders. Such mixture composition was

* **Corresponding author**
e-mail: beata.polak@umlub.edu.pl

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investigated for the first time. This purpose was determined by investigating the influence of surfactant, acetonitrile, and buffer pH and its concentrations on the migration time of the tested substances. The results were applied to the quantitative analysis and for the determination of investigated compounds in pharmaceutical prescriptions.

Table 1. UV spectra of investigated compounds

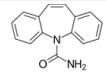
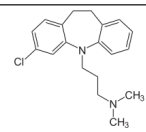
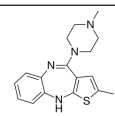
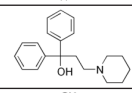
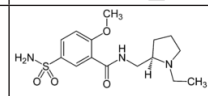
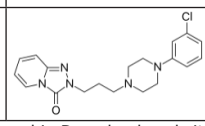


MATERIALS AND METHODS

The experiments were performed with an Agilent Technologies 7100 apparatus (Agilent Technologies, Redmond, Oregon, USA) equipped with a capillary (Agilent Technologies, Universal CE capillary, bare fused silica of 75 µm in diameter, 49 cm total length). Detection was performed with DAD at 200, 220 and 280 nm. Each zone of the investigated compounds was compared with its DAD spectrum to confirm the solute identity. The UV spectra of these are presented in Table 1.

Sulpiride, olanzapine, pridinol, clomipramine, trazodone, carbamazepine, and sodium dodecyl sulfate, (SDS) were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, USA). The chemical structures and physicochemical properties of investigated solutes are presented in Table 2.

Table 2. Names, structures, and physicochemical properties of investigated compounds

Compound/ drug group	formula	Log P value*	pKa value**
Carbamazepine/Antiepileptic/ analgesic/chemically related to tricyclic antidepressant; dibenzazepine		2.45	13.94
Clomipramine/Tricyclic antidepressant. Dibenzazepine		5.19	9.2
Olanzapine/Dopamine receptor antagonist; benzodiazepine		3.39	7.24
Pridinol; myorelaxant, benzene substituted derivatives		3.7	13.36 9.34
Sulpiride/ dopamine receptor antagonist (antipsychotics); benzene substituted derivatives		0.22	8.39
Trazodone/serotonin receptor antagonist. Diazine		2.9	7.09

*Log P and **pKa values were found in Drug-bank website (www.drugbank.com)

Boric acid and NaOH were purchased from POCH Avantor Performance Materials Poland S.A (Gliwice, Poland). Acetonitrile was obtained from Chempur (Piekary Śląskie, Poland). All reagents and chemicals used were of analytical reagent grade and employed as received without further purification. The appropriate pH borate buffer was prepared by potentiometric titration of 1M boric acid with 1M NaOH.

Pharmaceutical formulations: Amizepin 200 mg (Carbamazepine; manufacturer Polpharma), Ranofren 5 mg (Olanzapine; producer Adamed); Sulpiride 75 mg Teva and Anafranil SR 75 mg Teva (Clomipramine; (producer Teva), Tittico CR 75 mg (Trazodone, Angelini) and Pridinol 5 mg (Alvogen) were procured commercially.

The samples of the investigated compounds were obtained by dissolving the 1 mg of the solid in the methanol or methanol and a few droplets of distilled water. The final concentrations were 1 mg/mL. The samples for the calibration curves were prepared by weighing the proper mass of the sample and dissolving it in methanol or a mixture of methanol and distilled water and then mixed with the working buffer.

Preparation of pharmaceutical formulations for quantitative determination was performed according to the following procedure. Firstly, the tablet was crushed to powder with the mortar and pestle, then the powder was weighted and suspended in the methanol. The suspension was filtered using the quantitative filter, and, afterwards, the solution was mixed with the appropriate working buffer. Subsequently, it was introduced into the capillary.

The capillary was conditioned by rinsing the capillary several times with, firstly, 1 M NaOH (30 minutes), then 0.1 M NaOH (30 minutes), next, distilled water (30 minutes) and 0.1 M NaOH (45 minutes) and, finally, working buffer (30 minutes).

Analysis of the tested substance began by rinsing the capillary with 0.1 M NaOH for 5 minutes. The capillary was then rinsed successively with water and a working buffer for 5 minutes. After rinsing into the capillaries, a sample of the test substance was applied for 5 seconds.

The samples were hydrodynamically injected into the capillary. The injection pressure was 25-46 mBar, and the injection time was 5 seconds. The CE system temperature during all experiments was 25°C.

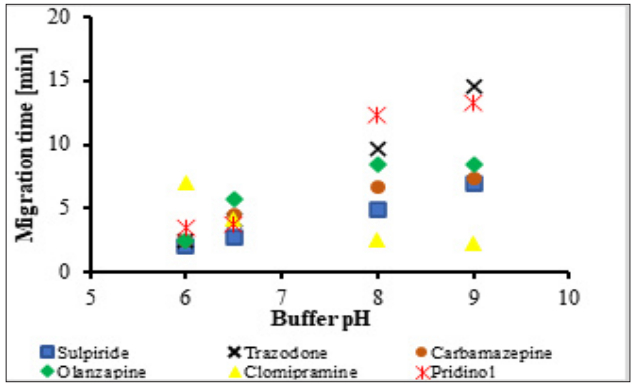
After dispensing the sample, the working buffer was dispensed into the capillary. The analysis was carried out until all peaks of the tested substances appeared. At the end of each test day, the capillary was rinsed for 20 min with distilled water.

RESULTS AND DISCUSSION

The migration time of substances in capillary electrophoresis depends on the type and strength of interactions between the tested substances and the stationary and mobile phases. Therefore, by changing the composition of the mobile phase, we can influence the migration time of individual components of the tested mixture and optimise the MEKC condition for its separation. Such a process for CE is presented in Figures 1-3 and Table 3.

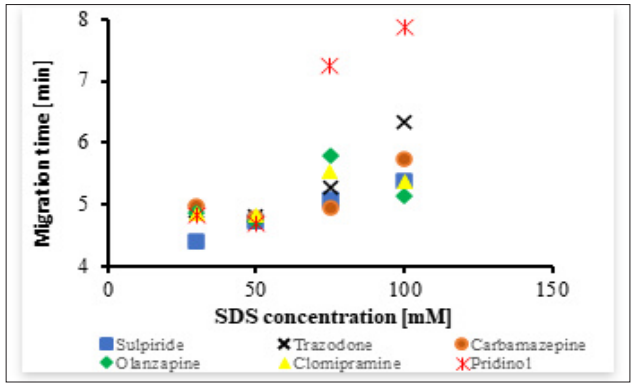
Since the solute migration time in CE depends on its ionisation [14-18], we investigated the influence of the buffer pH on the migration time (Figure 1). For this purpose, four buffer compositions of different pH from 6 to 9 were selected. However, the lower values of buffer pH were not scrutinised due to minute electroosmotic flow values and the need to perform the tests in conditions close to optimal within the TLC experiments [19] (systems containing lowered acidic pH buffer levels were applied to investigate tricyclic antidepressants in electrophoretic techniques and explored by Quirino [20,21] and Kowalski [22]).

The buffer pH range was below the pKa of the investigated solutes (see Table 1). Using the first two buffers with pH 6 and 6.5 resulted in the withdrawal of ionisation



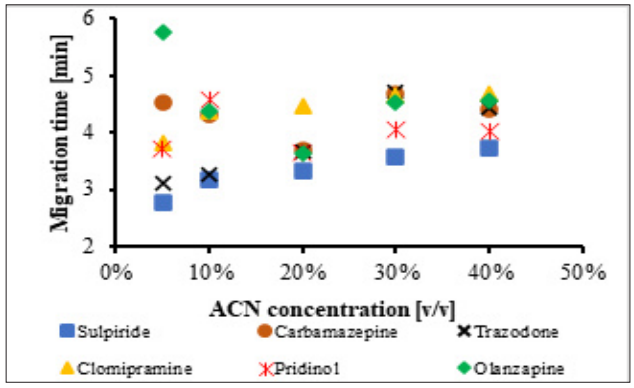
Composition of the running buffer: borate buffer (5% v/v), 50 mM SDS, 5% ACN. Separation conditions: applied voltage 20 kV, the capillary dimension 49 cm, i.d. 75 µm, detection at λ=200 nm, injection time 5 s, injection pressure 25-45 mBar.

Figure 1. The influence of borate buffer pH on the solute migration times



Running buffer composition: 20% acetonitrile, 15% borate buffer of pH 9 and various concentrations of SDS. Separation conditions: applied voltage 20 kV, the capillary dimension 49 cm, i.d. 75 µm, detection at λ=200 nm, injection time 5 s, injection pressure 25-46 mBar

Figure 2. The effect of SDS concentration on the investigated compound migration time



The running buffer composition: 50 mM SDS, 15% of borate buffer at pH 6.5. Experimental conditions: applied voltage 20 kV. Separation conditions: applied voltage 20 kV, the capillary dimension 49 cm, i.d. 75 µm, detection at λ=200 nm, injection time 5 s, injection pressure 25-46 mBar

Figure 3. The influence of acetonitrile concentration on the investigated solutes migration time

of almost all test substances (the exception was trazodone and carbamazepine, which remained neutral), while a buffer of pH 8 resulted in ionisation being withdrawn in the case of sulpiride and olanzapine. In contrast, pridinol and clomipramine were still ionized. At the buffer of pH 9, only clomipramine and pridinol remained ionized (the former only slightly). Carbamazepine, sulpiride, trazodone and olanzapine were in their neutral form at pH 9.

Table 3. The influence of the buffer concentration on the solute migration time

Solute	Migration time [min] at buffer concentration			
	5%	10%	15%	30%
	33.62 mM H_3BO_3 16.38 mM NaOH	67.25 mM H_3BO_3 32.75 mM NaOH	100.87 mM H_3BO_3 49.13 mM NaOH	201.75 mM H_3BO_3 98.25 mM NaOH
Sulpiride	3.165	4.185	4.721	5.345
Carbamazepine	3.091	4.55	4.777	5.455
Trazodone	3.501	4.515	4.811	5.555
Clomipramine	5.916	4.978	4.828	5.648
Pridinol	5.165	4.431	4.681	5.461
Olanzapine	4.625	4.604	4.885	5.578

Composition of the running buffer: borate buffer pH 9, 50 mM SDS, 20% ACN. Experimental conditions: applied voltage 20 kV, capillary 49 cm, i.d. 75 μm, detection at λ=200 nm, injection time 5 s

Since according to the micellar electrokinetic chromatography theory, the solute migration time depends on its charge, at the same buffer pH, the migration time for uncharged, neutral compounds is longer than for solute in its cationic form [23]. In our work, clomipramine significantly represents how the buffer pH affected solute migration (Figure 1). Its migration time was the longest at pH 6, and was enhanced when the buffer pH changed to 9.02, where it was the shortest at this buffer pH. The clomipramine charge demonstrated dramatic changing starting from buffer pH 8 (pKa for clomipramine is 9.2, Table 1), thus, we found it to be almost without charge at the last buffer pH. We noted that the migration time for the remaining solutes (with and without charge) was enhanced when the buffer pH increased. As for these, the migration time strongly depended on their hydrophobicity.

Thus, changing the buffer pH resulted in the varying electrophoretic mobility of investigated compounds, resulting in the system displaying selectivity. Selectivity was poor for the systems with the lowest buffer pH (6 or 6.5), but increasing the pH to 8 improved the outcome of the experiment. Except for the solute hydrophobicity, the second feature was seen to be also responsible for such a situation. Increasing the buffer pH also caused the ionisation of the silanol groups (capillary walls), enhancing the electroosmotic flow (EOF) [18,23].

The migration order for the buffer of pH 6.5 was as follows (according to the migration time increasing): sulpiride < pridinol < trazodone < clomipramine < carbamazepine < olanzapine. This order significantly differed from TLC experiments performed at similar buffer pH [19].

As mentioned earlier, the best solute zone separation was reached for buffer pH 8 and 9. The migration order for pH 8 is as follows (according to the migration time enhancing): clomipramine < sulpiride < carbamazepine < olanzapine < trazodone < pridinol. As for pH 9, the only change is for the order of pridinol and trazodone.

Therefore, the buffer of pH 9 was chosen for further experiments in which we examined the influence of the SDS concentration on the solute's migration time. The results are presented in Figure 2. In micellar electrokinetic electrochromatography, the addition of a surfactant with a concentration greater than the critical micellar concentration (CMC), is to facilitate the separation of the test mixture [23]. When surfactants are used in concentrations greater than CMC, they form micelles. Micelles are amphiphilic aggregates of molecules organised so that the hydrophobic tail of the molecule points inwards and the hydrophilic head faces the outside of the molecule [24]. Depending on the type of charge, surfactants move in or against the direction of the electroosmotic flow [23].

Sodium dodecylsulphate (SDS) is a basic surfactant in many MEKC experiments [14-17]. This was the main reason for choosing this surfactant for our research. The presented earlier experiments allowed us to establish the proper buffer pH (9.0) used in this part of the investigation. The range of SDS concentration applied in experiments was from 30-100 mM, and the running buffer contained 20% acetonitrile. The results are presented in Figure 2. We found poor compound zone separation for systems containing 30 and 50 mM of SDS, while good zone separation was obtained for 75 mM and 100 mM of SDS. However, the final concentration worsened the separation of clomipramine and sulpiride zones.

Under the above conditions, our work revealed that the velocity of the electroosmotic flow is greater than that of the moving SDS micelles, and the movement of the bulk phase is consistent with the movement of the EOF. Moreover, the neutral hydrophobic substances interact with the hydrophobic chains (hydrophobic core) of the SDS micelle, while SDS anions strongly attract the cations.

The order of the solute for the system containing 75 mM of SDS according to the migration time enhancement was as follows: carbamazepine < sulpiride < trazodone < clomipramine < olanzapine < pridinol.

We saw that the solute migration time is also affected by organic solvent content in the running buffer [14-16]. The influence of acetonitrile concentration on the migration time of the tested substances was examined in the subsequent investigations. The results are presented in Figure 3. The tested running buffer conditions were as follows: 50 mM of SDS, a buffer of pH 6.5 and acetonitrile content from 5 to 40 % v/v. The experiments demonstrated that the increase of the acetonitrile concentration in the range from 5 to 30% resulted in elongating of the solute migration times. In related work, such effects were also observed for steroids [15]. In our experiments, further growth of the organic solvent above 30% had little influence on the solute migration time. Nevertheless, the changes in the acetonitrile content in the running buffer affected the separation of the solute zones and worsened it at higher concentrations of this modifier. It also was found to influence the order of the migrated compounds. The best solute zone separation was reached at a small acetonitrile concentration.

By selecting the appropriate chemical composition of the running buffer, it is possible to control the selectivity of the separation of components. In previous work, changing the concentration or ionic strength of the buffer was found to affect the electrokinetic potential [25], and the increase in the concentration and ionic strength of the buffer was noted to decrease the electrokinetic potential and electroosmotic flow [25]. However, the continuous increase of the buffer concentration harms the resolution of the tested system because,

with the increase of the buffer concentration, the released Joule heat increases, and thus the diffusion increases. For these reasons, the typical buffer concentration in the running buffer should be no higher than 100 mM [26].

The influence of the buffer concentration on the solute migration distance was assessed using the mobile phase containing 20% acetonitrile, 50 mM SDS and various concentrations (from 5% to 30%) of the borate buffer at pH 9. In our study, the change in buffer concentration ranged from 50 to 300 mM. Thus, the investigation of this parameter on the migration time was crucial. The effect of buffer concentration on migration time is shown in Table 3. Thus, the solute migration times are enhanced with a rise in the buffer content. Unfortunately, this phenomenon was not accompanied by the enhancement in the compound zone separation. Thus, the poorest system selectivity was observed for 30% of the buffer content. Therefore, the buffer content in the 5 to 15% range was chosen for further tests.

Running buffers with different ACN, SDS and buffer contents were tested during our previous experiments. The best results were obtained with the mobile phases containing 19% ACN, 75 mM SDS and a buffer of pH 9. By modifying the buffer concentration, the best separation was obtained with the mobile phase containing 19% ACN, 75 mM SDS and 15% borate buffer at pH 9. The optimal separation of the investigated solute mixture is presented in Figure 4. The peak pair resolution Rs factors were as follows: sulpiride/clomipramine Rs = 2.58, clomipramine/carbamazepine Rs = 12.54, carbamazepine/trazodone Rs = 13.63, trazodone/pridinol Rs = 16.59 and pridinol/olanzapine Rs = 11.76.

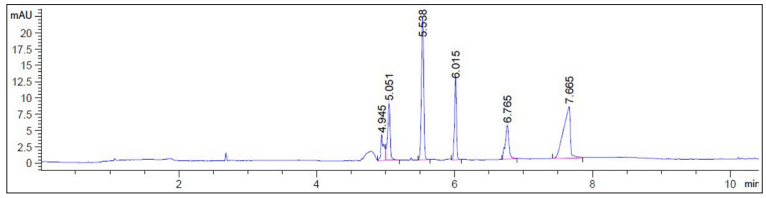
In the next part of the experiments, we determined the influence of the chosen separation method in its optimal condition on the separation efficiency and zone shapes of the separated mixture.

As for the separation efficiency, the system efficiency was presented as the number of the theoretical plates, N. Peak symmetry was calculated by the equipment software (Agilent ChemStation 3D-CE). The results are presented in Table 4. The separation efficiency, N, was in the range of 18216-374391. These results confirmed the main advantage of electrophoretic systems – mainly, high separation efficiency. Regarding peak symmetry, according to the calculations, the olanzapine and sulpiride peaks were asymmetric.

Table 4. The effect of the separation conditions in MEKC on the separation efficiency and solute peak asymmetry calculated by Agilent ChemStation 3D-CE

Compounds	Separation efficiency, N	Peak symmetry
Carbamazepine	293214	1.05
Clomipramine	30708	1.30
Olanzapine	19004	3.87
Sulpiride	18216	0.40
Pridinol	374391	1.08
Trazodone	101146	1.04

The figures of merit for the method are presented in Table 5 according to the information from [23,27]. The concentration



Composition of the mobile phase: 15% borate buffer of pH 9, 19% ACN, 75 mM SDS. Separation conditions: applied voltage 20 kV, the capillary dimension 49 cm, i.d. 75 μm, detection at λ=200 nm, injection time 5 s, injection pressure 25-45 mBar

Figure 4. Electrochromatogram of mixture separation

of solutes ranged from 0.0125 (trazodone) to 0.8 (sulpiride) mg/mL. The determined linear regression equations for all tested compounds determined had a correlation coefficient close to 1.0, which confirmed the linear response of the detector on the solute content. In the next step of the research, the limits of detection (LOD) and quantification were determined. The lowest LOD and LOQ values were determined for clomipramine (0.0127 and 0.0384 mg/mL, respectively), while the highest LOD and LOQ were for pridinol (0.1398 and 0.4237 mg/mL, correspondingly).

Table 5. Figures of merit for MEKC separation

Compound	Concentration range mg/mL	Linear equation	R2	LOD [mg/mL]	LOQ [mg/mL]
Carbamazepine	0.100-0.500	Y=4039.2x-32.52	0.9993	0.03731	0.1131
Clomipramine	0.015-0.050	Y=12297x+137.39	0.9929	0.0127	0.0384
Olanzapine	0.050-0.500	Y=11524x-354.49	0.9968	0.0734	0.2224
Pridinol	0.100-0.500	Y=10107x-301.66	0.9903	0.1398	0.4237
Sulpiride	0.050-0.800	Y=1286.3x-2.3851	0.9901	0.0189	0.0574
Trazodone	0.0125-0.200	Y=17490x+407.75	0.9971	0.0237	0.0718

Mobile phase 75 mM of SDS, 19% acetonitrile; 15% buffer of pH 9.0; other experiment conditions like in Table 3

The intraday repeatability for CE was assessed for three concentration levels for each scrutinized compound, presented as %RSD in Table 6. They were in the range of 1.8 to 5.3%. The average % RSD was 2.92.

Table 6. Repeatability of MEKC measurement

Solute	Sample concentration [mg/mL]	Intraday repeatability n=3	RSD [%]
Carbamazepine	0.400	1593.5±35.47	2.2
	0.300	1178.7±21.94	1.8
	0.200	748.5±22.94	3.0
Clomipramine	0.050	737±21.86	2.9
	0.040	640±21.9	5.3
	0.035	586±19.26	3.2
Olanzapine	0.400	4150±129.58	3.1
	0.200	1804±60.78	3.3
	0.100	872.4±31.53	3.6
Pridinol	0.400	3480±83.25	2.3
	0.300	2814±69.03	2.4
	0.200	1797±51.06	2.8
Sulpiride	0.800	990±32.46	3.2
	0.500	678±16.37	2.4
	0.300	432±12.17	2.8
Trazodone	0.100	2182±59.61	2.7
	0.050	1272±27.46	2.1
	0.025	739±25.63	3.4

Running buffer: 75 mM of SDS, 19% acetonitrile; buffer of pH 9.0 (15%). Separation conditions: applied voltage 20 kV, capillary 49cm, i.d. 75 μm, detection at λ=200 nm, injection time 5 s

The drug contents in pharmaceutical samples were investigated to assess the technique application for real sample analysis. For this purpose, the determined earlier optimal running buffer composition was applied. The results are presented in Table 7 in terms of % of the measurement errors, intraday precision (standard deviation) and the % RSD.

Table 7. Determination of investigated compounds in pharmaceutical formulations by MEKC

Compound, Pharmaceutical formulation (manufacturer)	% Error between determined and declared amount	Intraday precision of zone area	RSD [%]
Olanzapine, Ranofren 5 mg (ADAMED)	2.00	2616±65.39	2.5
Sulpiride Sulpiryd Teva 75 mg (Teva)	1.14	520±12.48	2.4
Carbamazepine, Amizepin 200 mg (Polpharma)	0.44	12285±27.03	2.2
Trazodone TritticoCR 75 mg (Angelini)	1.90	13084±83.74	6.4
Pridinol Pridinol 5 mg (Alvogen)	1.10	2326±69.77	3.0
Clomipramine Anafranil SR 75 mg (Teva)	2.33	499±26.94	5.4

In such mode, the determined content of the researched compounds in the tablets deviated from the declared by 0.44 to 2.33%. The lowest deviation from the declared content was for carbamazepine and the highest for clomipramine formulations. The % RSD for the measurement was in the range of 2.2 to 6.4. These results showed that the method could be applied to quantitatively determine the real drug samples.

CONCLUSIONS

Micellar systems of capillary electrophoresis have been explored by several researchers for their usefulness in assessing the effectiveness of drugs against neurodegenerative problems. Such practices usually involved the micelle to solvent stacking mode of investigated compounds application, and the experiments were conducted in acidic buffer pH and organic solvents (methanol or acetonitrile). However, the investigations have been limited to one or two classes of drugs.

In the presented method, we performed experiments in a running buffer containing a micellar SDS system with a borate buffer of pH 9.0. As a result, we were able to separate representatives of various classes of drugs (tricyclic antidepressants (carbamazepine and clomipramine), dopamine receptor antagonists (olanzapine and sulpiride), serotonin receptor antagonists (trazodone) and myorelaxant (pridinol)) which are usually used in combined therapy. The baseline separation of the mixture was performed within 8 min. The used acetonitrile concentration was 19%, per the principles of MEKC.

The optimised running buffer conditions allowed for the quantitative determination of all investigated drugs. The figures of merit for the method were presented employing linearity, LOQ and LOD values, and %RSD values were acceptable for the majority of investigated solutes (less than 5%). Thus, quantitative determination of all investigated compounds in pharmaceutical formulations with satisfactory error levels was achieved.

ORCID iDs

Kamila Jaglińska https://orcid.org/0000-0002-3309-6526
Beata Polak https://orcid.org/0000-0003-4237-648X

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