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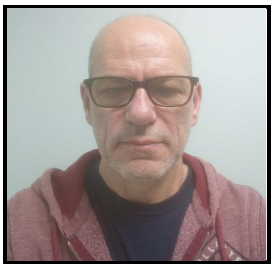

DEVELOPMENT OF A SIMPLE AND ROBUST METHOD FOR DETERMINATION OF DOXYCYCLINE AND AMPICILLIN BY CAPILLARY ELECTROPHORESIS IN DRUGS PURCHASED IN LAO PDR AND CAMBODIA

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ABSTRACT

We describe a simple and robust analytical method based on capillary electrophoresis for qualitative and quantitative analysis of two antibiotics, doxycycline and ampicillin, that were purchased in Lao PDR and Cambodia. Alow-cost capillary electrophoresis apparatus, originally developed for teaching purposes and/or operating in remote areas and harsh conditions, was utilized in this study. Analyses of the two antibiotics were performed in an uncoated fused-silica capillary filled with a sodium phosphate buffer (10mM; pH = 2.3). The solute detection was accomplished by UV absorption at 200nm. Histidine was employed as an internal standard and the correlation coefficients of doxycycline and ampicillin were determined as 0.9997 and 0.9992, respectively. In total, 18 samples of doxycycline and 19 samples of ampicillin were analyzed. Among the 18 doxycycline samples, only two had a percentage of active pharmaceutical ingredient content that did not fall inside the 85% - 115% range, while we found 13 out of 19 ampicillin samples that were out of this range. We also analyzed doxycycline and ampicillin obtained from a pharmacy in France, as two control samples, and in both cases we found the percentage of active ingredient content close to 100% (98, 9% for doxycycline and 98, 3% for ampicillin). This study was carried out as part of a training process, initiated by Pierre-Fabre foundation, of two PhD students from Lao PDR and Cambodia that will integrate this method into a teaching process at pharmacy schools in their respective countries.

KEYWORDS

Capillary electrophoresis, Doxycycline and Ampicillin.

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INTRODUCTION

Doxycycline is a broad spectrum antibiotic that belongs to the class of tetracycline family and is commonly employed for the treatment of various bacterial and parasite infections, for instance malaria and early stages of Lyme disease[1,2]. Ampicillin is also a broad spectrum antibiotic

commonly employed to treat a number of bacterial infections, such as urinary, gastro-intestinal and respiratory ones and bacterialmeningitis[3,4]. Both antibiotics are on the List of Essential Medicines of World Health Organization (WHO)[5] and they are available as generic and inexpensive drugs.

Antibiotics belong to the class of drugs that are especially important in the developing world, like South Asia region, sub-Saharan Africa and Latin America, where infection diseases still remain the prevalent cause of death[6-8]. It is well known that in this part of the world, antibiotics can be purchased in pharmacies without medical prescription that leads to self-medication and it increases the risk of in appropriate drug use and, consequently, development of microbial resistance. Increased use of antibiotics together with less regulations and weaker anti-counterfeit laws in these regions rise concerns that antibiotics, among other drugs, could be potentially contaminated with substandard and counterfeit medicines[9-11]. Analogously, in the growing importance of internet marked today, counterfeit medicines become a real threat to the health and safety of patients not only in the regions where they are manufactured but around the entire world[12]. Almost 50% of sold drugs in some on-line pharmacies are counterfeit or substandard. The producers of substandard and counterfeit medicines spend a non-negligible amount of money on packaging to make it harder to identify such drugs rapidly and easily. Therefore, analytical/chemical methods need often be utilized for qualitative and quantitative determination of the active pharmaceutical ingredients (API) and excipients.

Among chemical methods for rapid drug screening, colorimetric assays are often employed since they are simple, inexpensive and fast, however, they may yield in false-positive results due to a low-specificity[13-15]. On the other hand, spectroscopic techniques, such as Fourier-transform infrared (FT-IR) and near infrared (NIR) spectroscopies, Raman spectroscopy and nuclear magnetic resonance (NMR) spectroscopy are non-destructive techniques that provide a rich information on the molecular structure, but they often lack in sensitivity and require well trained operators[16-20]. Direct mass spectrometry techniques[20-22] are also frequently employed for drug analysis as they are very fast, highly sensitive and provide a rich structural information but they are expensive and require complex quantitation procedures. Separation techniques such as thin layer chromatography (TLC)[23], high-performance liquid chromatography with UV or mass spectrometry detection (HPLC)[14,24-27] and capillary electrophoresis (CE)[28-31] are ones of the most commonly used chemical methods for drug analyses today. While chromatography methods provide excellent selectivity and sensitivity, the important consumption of organic solvents and samples as well as generation of large volumes of mobile phases contaminated with samples present difficulties when working in conditions with restricted access to chemicals and laboratory resources. On the other hand, CE although it lacks the sensitivity of LC and LC-MS methods, is very interesting for analyses of pharmaceuticals[14,15] due to its simplicity, robustness and small volumes of samples (in order of pico-liters) and electrolytes consumed.

We utilized in this study a CE apparatus that is a low-cost, simple to operate (all the parameters are manually controlled) and robust, suiting thus well to operate in remote areas with limited technical support[16]. While the poor concentration sensitivity of a UV detection in CE can be an important drawback for certain application, this is not a problem for drug analyses since solutions of injected samples can be prepared in an optimal concentration range for a given detector. The two antibiotics were detected by UV-absorption at 200nm and the separations were carried out in a low concentration (10mM) and low pH (2.3) phosphate buffer. The acidic pH improved solutes solubility, minimized electro osmotic flow and decreased adsorption of the antibiotics on the inner capillary wall. Moreover, the phosphate buffer is inexpensive, stable at room temperature and it eliminates the need for capillary coating which leads to an increased capillary life time and decreased running costs.

MATERIAL AND METHODS

CE apparatus was obtained from Wynsep (Toulouse, France) and UV-Vis spectrophotometer, Specord 205 was acquired from Analytik Jena AG (Jena, Germany). Fused-silica capillaries (380µm outer diameter, 50µm inner diameter) were purchased from Polymicro Technologies (Austin, TX, USA). Phosphoric acid, sodium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, histidine, doxycycline monohydrate and ampicillin were obtained from Sigma-Aldrich (Saint-Quentin Fallavier, France). Doxycycline and ampicillin tablets and capsules were purchased in Lao PDR and Cambodia (Table No.1a and No.1b), except for the doxycycline from Mylan and ampicillin (Unicem) from Pfizer that were purchased in a pharmacy in Toulouse (France). The doxycycline from Mylan and the ampicillin from Pfizer were used as standards to validate our method.

Sodium phosphate buffer (10mM, pH 2.3) was utilized for all the experiments performed in this work. We prepared five standard solutions of doxycycline and ampicillin respectively in the concentration range between 40 and 200mg/L. These solutions were employed for construction of the calibration curves. The sample solutions (tablets and capsules of doxycycline and ampicillin) were prepared in such a way that the final, theoretical concentration of API in each sample was 100mg/L. We added histidine at a final concentration of 100mg/L to all analyzed solutions that served as internal standard and phosphoric acid (final concentration 10mM) in order to improve solubility of the antibiotics. The samples were injected by pressure during 5s at 50m bars and detected by UV absorption at 200nm. The electrophoregrams were analyzed with Clarity 7.2 software (Data Apex Ltd., Czech Republic).

RESULTS AND DISCUSSION

Typical electrophoregrams of doxycycline and ampicillin are shown in Figure No.1a and No.1b. Doxycycline migrated slightly faster than ampicillin at these experimental conditions and the two antibiotics could easily be separated from each other if they were present together in a same sample. The peak of histidine (internal standard), that migrated considerably faster than Doxycycline and Ampicillin, can also be seen in the electrophoregrams (Figure No.1a and No.1b). Calibration curves for doxycycline and ampicillin are shown in Figure No.2a and No.2b. We decided to construct calibration curves in a relatively high-end range of concentrations (between 40 and 200mg/L) because of the poor concentration sensitivity of a UV detection in CE separation (due to the small inner diameters of used capillaries). The correlation coefficients were 0.9997 and 0.9992 for doxycycline and ampicillin respectively, indicating an excellent peak area/concentration linearity. The correlation coefficients were somewhat smaller when histidine was not used (results not shown).

The results of all analyzed samples are summarized in the Table No.2a (doxycycline) and Table No.2b (ampicillin). For doxycycline, only two samples (sample number 4 and 8, see Table No.1a) are out of the 85-115% API range and 9 samples fall in the 95-105% API range. The situation is somewhat less satisfactory for ampicillin where 13 out of 19 analyzed samples are out of the 85-115% API range, while only two samples satisfy the 95-105% API range. Interestingly, we systematically found less than 100% of API in all ampicillin drugs that we analyzed. To validate our method, we analyzed one doxycycline and one Ampicillin drug purchased in a pharmacy in France (100mg doxycycline tablets from Mylan and 1000mg Ampicillin powder (Unacim) from Pfizer (see Tables No.2a and No.2b)). For the Doxycycline sample, we found 98.69mg (98.9%) of API, while for ampicillin we found 983.26mg (98.3%) of API, which is quite satisfactory for quantitative determination performed on a capillary electrophoresis instrument. All the solutions were analyzed three times and the standard deviations are given in Table No.2a and No.2b.

Only the sample number 8 did not fall in the 85-115% range of API. As a control, we analyzed a doxycycline in tablets purchased in France (Mylan) and we found 98.7% of API, which is a satisfactory result.

In total, 9 samples (1, 2, 4, 6 - 11) did not fall in the 85-115% range of API. As a control, we analyzed an ampicillin powder purchased in France (Pfizer) and we found 105.7% of API, which is relatively high.

Table No.1a: List of doxycycline drugs purchased in pharmacies in Lao PDR and Cambodia

Sample #	Dose (mg)	Type	Factory	Lot #	Expiration Date	Country
1	100	capsule	Codupha-Lao PDR	612201	January-2019	Lao PDR
2	100	capsule	Codupha-Lao PDR	612203	Jully-2019	Lao PDR
3	100	capsule	Bangkok Lab amd Cosmetic	L618	April-2021	Lao PDR
4	100	capsule	Bangkok Lab and Cosmetic	L465	June-2020	Lao PDR
5	100	capsule	Bangkok Lab and Cosmetic	L334	Mars-2019	Lao PDR
6	100	capsule	T.MAN Pharma	7985603	August-2017	Lao PDR
7	100	capsule	Chumchon	14H083	August-2017	Lao PDR
8	100	capsule	Codupha-Lao PDR	412204	August-2017	Lao PDR
9	100	capsule	Bangkok Lab and Cosmetic	L120	April-2020	Lao PDR
10	100	capsule	Bangkok Lab and Cosmetic	L883	May-2021	Lao PDR
11	100	tablet	Bailly-Creat	49	Mars-2020	Cambodia
12	100	capsule	Bangkok Lab amd Cosmetic	L120	April-2020	Lao PDR
13	100	capsule	Codupha-Lao PDR	512203	April-2018	Lao PDR
14	100	capsule	Hovid	bj01692	December-2020	Cambodia
15	100	capsule	Medico	cbc309	September-2018	Cambodia
16	100	capsule	MS	71799	November-2020	Cambodia
17	100	tablet	Bailly-Creat	51	November-2020	Cambodia
18	100	tablet	Bailly-Creat	43	January-2019	Cambodia

Table No.1b: List of ampicillin drugs purchased in pharmacies in Lao PDR and Cambodia

Sample #	Dose (mg)	Type	Factory	Lot #	Expiration Date	Country
1	500	capsule	Codupha-Lao PDR	600929	September-2019	Lao PDR
2	500	capsule	KPN Pharma	1645027	October-2019	Lao PDR
3	500	capsule	Codupha-Lao PDR	600902	January-2019	Lao PDR
4	500	capsule	KPN Pharma	1645022	August-2019	Lao PDR
5	500	capsule	KPN Pharma	1645023	August-2019	Lao PDR
6	500	capsule	Codupha-Lao PDR	600930	September-2019	Lao PDR
7	500	capsule	Codupha-Lao PDR	600918	Jully-2019	Lao PDR
8	500	capsule	Codupha-Lao PDR	600923	September-2019	Lao PDR
9	250	tablet	Codupha-Lao PDR	400711	November-2017	Lao PDR
10	250	tablet	Codupha-Lao PDR	600720	January-2019	Lao PDR
11	250	tablet	Codupha-Lao PDR	600715	June-2019	Lao PDR
12	500	capsule	Bailly-Creat	ap14	May-2019	Cambodia
13	500	capsule	Laboratory-EPHAC	62084	December-2019	Cambodia
14	500	capsule	Bailly-Creat	hc6152	April-2020	Cambodia
15	500	capsule	MS	67006	January-2019	Cambodia
16	500	capsule	Bailly-Creat	hg6461	Jully-2020	Cambodia
17	500	capsule	Bailly-Creat	ap11	February-2019	Cambodia
18	500	capsule	Medopharm PVT	18197002	December-2020	Cambodia
19	500	capsule	Laboratory-EPHAC	72017	February-2019	Cambodia

Table No.2a: Results of the quantitative determination of doxycycline in samples purchased in pharmacies in Lao PDR, Cambodia and France

Sample #	% API
1	90.7 ± 3.9
2	82.8 ± 0.8
3	105.7 ± 3.4
4	116.9 ± 2.0
5	107.4 ± 3.2
6	105.5 ± 3.7
7	107.4 ±5.8
8	76.3 ± 4.7
9	103.9 ± 5.3
10	97.3 ± 2.7
11	99.6± 2.0
12	105.8 ± 2.7
13	101.9 ± 1.0
14	99.8 ± 5.5
15	99.9 ± 5.9
16	98.2 ± 3.4
17	99.6 ±4.0
18	94.8 ± 0.6
Mylan	98.9 ± 2.0

Table No.2b: Results of the quantitative determination of ampicillin in samples purchased in pharmacies in Lao PDR, Cambodia and France

Sample #	% API
1	73.8 ± 2.5
2	77.1 ± 4.4
3	82.9 ± 3.9
4	78.5 ± 3.7
5	82.8 ± 1.5
6	80.0 ± 2.4
7	79.0 ± 3.7
8	76.6 ± 0.2
9	68.4 ± 3.8
10	77.1 ± 4.2
11	78.2 ± 3.1
12	93.4 ± 4.4
13	96.5 ± 5.6
14	93.8 ± 2.1
15	83.8 ± 4.8
16	88.3 ± 2.9
17	86.7 ± 1.3
18	82.7 ± 4.1
19	91.2 ± 5.8
Pfizer (Unacim)	98.3 ± 1.7

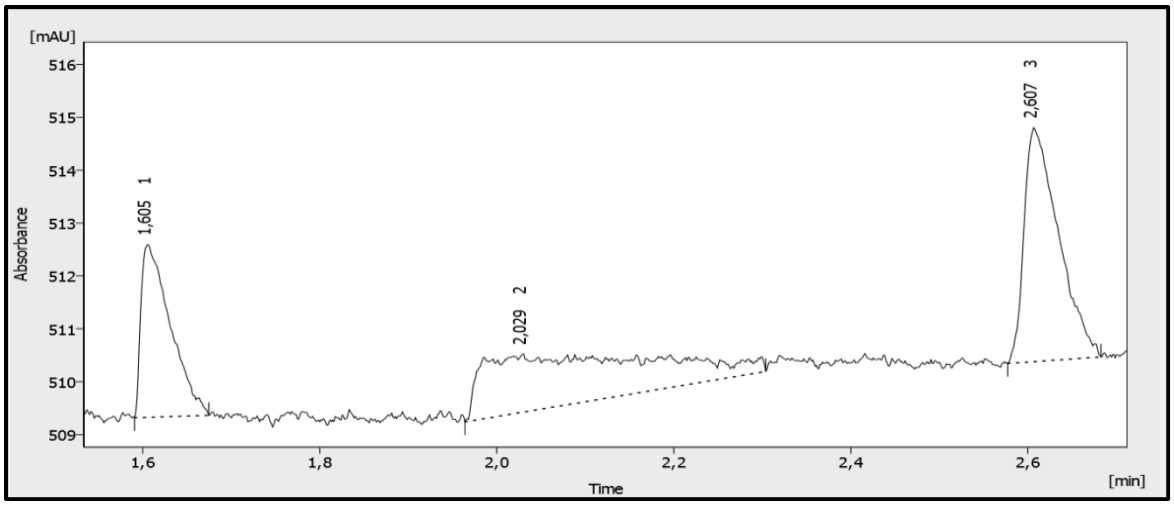

Figure No.1a: A typical ellectrophoregram showing a peak of doxycycline at 2.607 min and a peak of histidine (internal standard) at 1.605 min

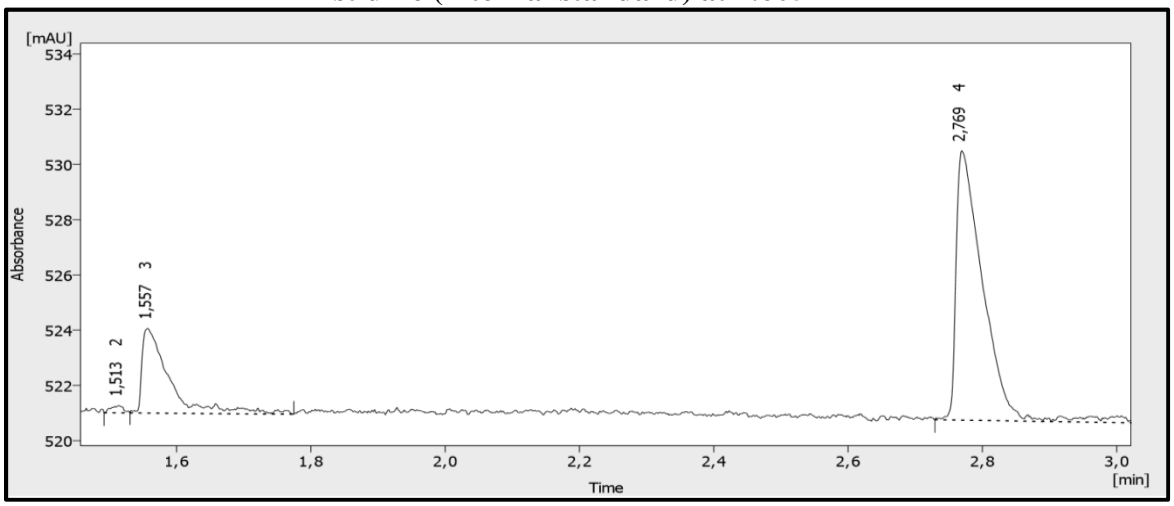

Figure No.1b: A typical electrophoregram showing a peak of ampicillin at 2.769 min and a peak of histidine (internal standard) at 1.557 min

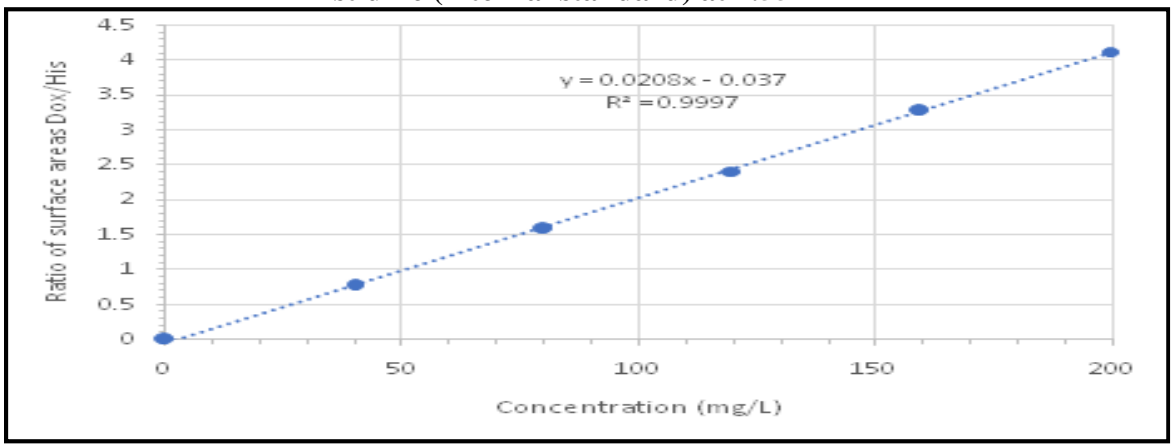

Figure No.2a: Calibration curve of doxycycline. We prepared 5 solutions of doxycycline in 10mM phosphoric acid in the concentration range from 40 to 200mg/L. We added histidine as internal standard into each solution at a final concentration of 100mg/L

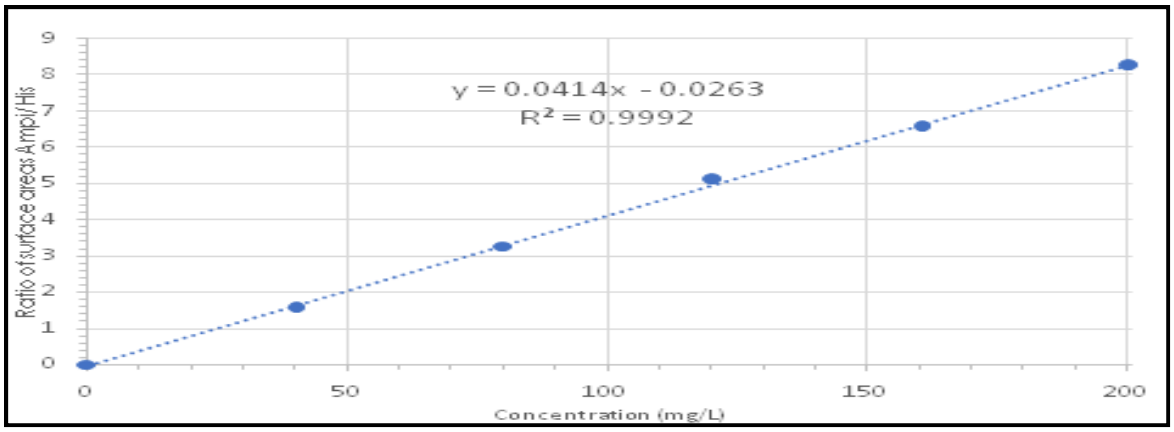

Figure No.2b: Calibration curve of ampicillin. We prepared 5 solutions of Ampicillin in 10 mM phosphoric acid in the concentration range from 40 to 200mg/L. We added histidine as internal standard into each solution at a final concentration of 100mg/L

CONCLUSION

We analyzed 37 antibiotic drugs (doxycycline and ampicillin) from Lao PDR and Cambodia by capillary electrophoresis. The experimental conditions were optimized in order to decrease the cost per analysis and to improve robustness of the utilized method. The low concentration and low pH phosphate buffer employed in this study was essential to solubilize the antibiotics and to minimized adsorption of the samples on the capillary inner surface (noting that uncoated capillaries were utilized in this study). Wynsep CE apparatus was employed for all the samples that were analyzed in this work. The apparatus is very simple and robust and it was designed to perform well in laboratories with sub-standard working conditions. The instrument exists only in the manual version and it is not very practical and user-friendly when many samples need to be analyzed. On the other hand, it is very easy and handy to change the running voltage and the acquisition time as well as the parameters of the sample injection, however, keeping a memory of experimental conditions during an optimization process may be time consuming and difficult. From all the samples that we analyzed, we found only two samples (sample # 4 and 8) of doxycycline that felt out of the 85-115% API range. The situation was less satisfactory with the Ampicillin samples as we found 13 out of 19 samples that felt out of the 85-115% API range and only two samples that satisfied the 95-105% API range. Also, the quantity of ampicillin found in all analyzed samples was systematically less that the quantity indicated on the packaging. Considering our standard samples, we found 98.9% of API in the doxycycline from Mylan and 98.3% of API in the ampicillin from Pfizer, which is s satisfactory result.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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