Journal of Pharmaceutical and Biomedical Analysis 158 (2018) 405–415

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Review

Recent advances in the capillary electrophoresis analysis of antibiotics with capacitively coupled contactless conductivity detection

Prasanta Paul[a], Cari Sänger-van de Griend[b,c], Erwin Adams[a], Ann Van Schepdael[a,*]

[a] KU Leuven - University of Leuven, Pharmaceutical Analysis, Department of Pharmaceutical and Pharmacological Sciences, O&N2, PB 923, Herestraat 49, Leuven, 3000, Belgium
[b] Department of Medicinal chemistry, Uppsala University, Husargatan 3, Uppsala, 751 23, Sweden
[c] Kantisto BV, Callenburglaan 22, Baarn, 3742 MV, The Netherlands

ARTICLE INFO

Article history:
Received 12 May 2018
Received in revised form 18 June 2018
Accepted 19 June 2018
Available online 20 June 2018

Keywords:
Capillary electrophoresis
Capacitively coupled contactless conductivity
Portable devices
Antibiotic
Review

ABSTRACT

This review describes briefly the high rate of counterfeiting of antimicrobial drugs with focus upon its immediate health consequences. The major part of this review encompasses accounts of the improvements achieved in the domain of miniaturization of capillary electrophoresis with capacitively coupled contactless conductivity detection (CE-C^4D). The application of this principle into the development of portable devices as well as its application to counter the health-system-crippling phenomenon of counterfeit antibiotic formulations, are discussed in the context of developing countries.

Contents

Abbreviations: WHO, World Health Organization; UNODC, United Nations Office on Drugs and Crime; CD, conductivity detection; C^4D, capacitively coupled contactless conductivity detection; AC-DC, alternating current to direct current; LIF, laser induced fluorescence; BGE, background electrolyte; Q_bD, quality by design; MES, 2-(N-morpholino) ethane sulfonic acid; CTAB, cetyltrimethylammonium bromide; TRIS, tris(hydroxymethyl)aminomethane; TAPS, tris(methylamino)propanesulfonic acid; EOF, electroosmotic flow; BIA, batch injection analysis.

* Corresponding author.
E-mail address: Ann.VanSchepdael@kuleuven.be (A. Van Schepdael).

https://doi.org/10.1016/j.jpba.2018.06.033
0731-7085/

1. Introduction

Counterfeit and substandard medicines are two phenomena which have been studied extensively in the past. They are prevalent, not only in developing countries, but increasingly becoming ubiquitous in the developed countries as well. The spread of fake drugs is a multifactorial process with significant contributions stemming from diverse sources, ranging from the unawareness and negligence of the patient to the corruption inflicted government agencies [1]. Additionally, internet-based on-line purchase of medicines and fitness products by the patient is contributing to the growing cases of falsified drugs in industrialized countries [2,3]. A survey suggested that half of the on-line purchased drugs are counterfeit [1]. Though drug falsification accounts for 1% of the pharmaceutical market in the developed countries, the reported cases have been steadily increasing in Europe and the US [4].

Published data report the magnitude of drug falsification, ranging from 1 to 30% of the marketed drugs. The scenario in the middle and low-income countries is even worse. Several reports suggested a surprisingly high level of drug counterfeiting (~ 75%) in some African countries including Nigeria. The official statistics from WHO revealed a scary magnitude of drug counterfeit of 25%. This figure is way higher than global estimates (10%) of reported incidents (http://www.who.int/mediacentre/factsheets/fs275/en/).

However, those estimates are not concrete because of the limited number of published researches concerning drug counterfeiting [4]. Frequently, the counterfeit-related incidents appear in newspapers and other online resources rather than the biomedical literature. Additionally, much of the ambiguity around the cases of poor drug quality/counterfeit drugs are due to restriction on the accessibility and reluctance by the pharmaceutical and regulatory authorities to publish. However, counterfeit prevalence studies from the national and international organizations still constitute the authentic source of drug falsification estimates.

All categories of drugs are vulnerable to counterfeiting. Kelesidis et al. have summarized the counterfeit prevalence of antimicrobial drugs worldwide [4,5]. Numerous publications reported significant falsification of antimicrobials that could go as high as 50% of the worldwide fake drugs. Developing countries account for the majority of antibiotic falsification (78%), an appallingly high rate which undermines already insufficient public healthcare. According to WHO and the United Nations Office on Drugs and Crime (UNODC), the major sources of those substandard or counterfeit antimicrobial drugs are coming from India, China and Thailand. A review on antibiotic counterfeiting indicated an alarming rate of 44%, 30% and 9% in Asia, Africa, and Europe and North America, respectively [6]. Among the antibiotic counterfeits, β-lactam antibiotics account for 50% of the cases followed by quinolones (12%), macrolides and lincosamides (11%), tetracyclines (7%) and others (20%) [6].

Assurance of providing quality medicines is key to public healthcare worldwide [7]. The dosage of drugs prescribed is crucial for the therapy of certain diseases like microbial infections. A sub-potent dose administration of drugs (antibiotics) increases the chance of therapeutic failure through microbial genesis of resistance thereby increasing the burden on the healthcare system [8–10]. Resource constraint developing countries suffer in their healthcare system from a lack of analytical and distribution infrastructure to monitor and regulate the quality of medicines until the end user. In poor nations like those from western Africa and some parts of Asia, infectious diseases are a common health issue and logically demand high proportions of anti-infective medications for treating them. Consequently, those medications are in particular susceptible to drug counterfeiting [6,11–14].

The quality of medicines is ensured through the implementation of quality control (QC) and Good Manufacturing Practices (GMP) [15]. The monographs for quality control of almost all available drugs are reported in different pharmacopoeias. Most of the methods are based on sophisticated analytical tools, for example gas chromatography (GC) or liquid chromatography (HPLC) hyphenated to different detection systems (UV, mass spectrometry, fluorescence, chemiluminescence etc). Apart from the large capital investment necessary for the acquisition of such techniques, high grade solvents required for those techniques, highly qualified technicians for maintenance, and the necessary infrastructure (air conditioning, humidity control, continuous electricity) to operate those equipments are not always available in the developing world.

Since constant quality control of medicines is essential for effective healthcare [16,17], measures needed to tackle drug counterfeiting are a highly critical issue in low and middle income countries. Hence, development of simple, robust, sensitive and economic analytical alternatives that are able to be performed independent of laboratories and skilled staff is urgently needed.

Different techniques have already been introduced since the perception of necessity of simple, robust and sensitive tools in the 1980s. Different approaches (such as kit based techniques) have been implemented already, but met with little success. Most recently, capillary electrophoresis (CE) based methods are proposed as an economic and efficient alternative to HPLC to combat drug counterfeiting [18]. In this review, we describe CE as a potential analytical tool for miniaturization followed by a discussion on multiple aspects of improvements achieved in the detection system as well as its application in the determination of antimicrobial medication.

2. CE with conductivity detection

CE is a straightforward technique requiring only a piece of capillary and minute amounts of solvent and sample. However, developing a robust CE method is not always easy since it is subject to multifactorial influence. CE is reported to couple different detection techniques and hence, method specific adaptation with respect to the detection unit is necessary for CE method development. UV detection is the common detection technique; however, the bulky size of the UV detector occupies a significant part of the equipment. Additionally, the decay of the UV lamp over time may result in increased replacement cost and may not be amenable for integration with portable and chip-based platforms of CE. The application of amperometry in CE analysis is also promising due to significant detection gain, but limited only to those compounds with redox potentiality [19]. Moreover, the fabrication of the amperometric device is not straightforward for the miniaturization of the CE-amperometry system. In contrast, conductometric detection (CD) is amenable to fit in the CE platform. The CD detector employs the measurement of conductance which is basically a bulk physical property of substances. This is the reason why CD is termed as a universal detection system. Unlike some of the previously mentioned detection units, CD structurally uses an electronic device. Different CD configurational strategies have been adopted in its early stages of development. The early CD configuration employed was direct electrode insertion into laser induced microholes on the capillary. A wall-jet configuration exploited the lowered background conductivity achieved through ion-exchange, a phenomenon which is alternatively called "suppressed CD". Other configurations reported for conventional CD are i) deposition of platinum at the capillary outlet [20] and ii) resistance measurement of liquid trapped by the hydrophilic polymer at the capillary end [21].

2.1. CE - capacitively coupled contactless conductivity detection

A relatively new approach termed, CE - capacitively coupled contactless conductivity detection (C^4D) has been proposed as an