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Review

A categorical review on electroanalytical determination of non-narcotic over-the-counter abused antitussive drugs

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ABSTRACT

Dextromethorphan (DXM) and diphenhydramine (DPH) are two commonly used over-the-counter non-narcotic antitussive drugs. Recent reports reveal the widespread abuse of DXM and DPH due to their euphoric and alcohol-like effects. Due to their medicinal importance as well as the apparent increase in their use as abused drugs, it has become critical to determine them in samples of biological, clinical and pharmaceutical interest. The electrochemical techniques for drug analysis have gathered considerable attention due to their pronounced selectivity, sensitivity and simplicity. The given review presents a compilation of published voltammetric and potentiometric methods developed for determination of DXM and DPH. It critically highlights the analytical performances, revealing the recent trends and progress in the specified approach for their analysis. The review forms a basis for further progress in this field and development of improved electrochemical sensors to determine the drug.

Contents

Abbreviations: AA, Acrylic acid; BEHS, Bis (2-ethylhexyl) sebacate; BIA, Batch injection analysis; BIA-MPA, Batch injection analysis system with multiple pulse amperometric detection; CDs, β-Cyclodextrins; CGE, Coated graphite electrode; CNP/CPE, Carbon nanoparticles-modified carbon paste electrode; CPE, Carbon paste electrode; CV, Cyclic voltammetry; CWE, Silver coated wire electrode; DBS, Dibutylsebacate; DOP, Dioctylphthalate; DPASV, Differential pulse anodic stripping voltammetry; DPH, Diphenhydramine; DPH-PL, Diphenhydramine-picrolonate; DPH-RN, Diphenhydramine-reineckate; DPH-TPB, Diphenhydramine-tetraphenylborate; DPV, Differential pulse voltammetry; DXM, Dextromethorphan; DXM-PM, Dextromethorphan-phosphomolybdate; DXM-RN, Dextromethorphan-reineckate; DXM-TPB, Dextromethorphan tetraphenylborate; DyNW/CPE, Dysprosium nanowire modified carbon paste electrode; EME, Electromembrane extraction; FFT-CV, Fast Fourier transform-cyclic voltammetry; FFT-SWV, Fast Fourier transform-square wave voltammetry; FIA, Flow injection analysis; GCE, Glassy carbon electrode; ICPE, Carbon paste electrode with sodium tetraphenyl borate ion pairing agent; ICPE, Ionic liquid based carbon paste electrode; INCPE, Carbon nanotube-carbon microparticle-ionic liquid composite carbon paste; IPs, Ion-pairs; ISEs, Ion-selective electrodes; ISPE, Screen-printed electrode with sodium tetraphenyl borate ion pairing agent; LOD, Limit of detection; LOQ, Limit of quantification; MCPE, Carbon paste electrode with DPH-TPB ion pair; MIP, Molecularly imprinted polymers; MSPE, Screen-printed electrode with DPH-TPB ion pair; NaTFPB, Sodium tetrakis (4-fluorophenyl) borate; NaTPB, Sodium tetraphenylborate; NCPE, Carbon nanotubes modified carbon paste electrode; NH4TPB, Ammonium tetraphenylborate; NIP, Non-imprinted polymers; o-NPOE, o-Nitrophenyl octyl ether; PCP, Phencyclidine; PHE, Phenylephrine; PMA, Phosphomolybdic acid; PT, Phosphotungstate; PTA, Phosphotungstic acid; PTp-CIPB, Tetrakis(p-chlorophenyl)borate; PVC, Polyvinyl chloride; RAS, Reineckate ammonium salt; RGO-SPCE, Reduced graphene oxide modified screen-printed carbon electrode; SPEs, Screen printed carbon electrodes; STA, Silicotungstic acid; TCP, Tricresylphosphate; THF, Tetrahydrofuran; TPB, Tetraphenylborate; VPY, Vinyl pyridine

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1. Introduction

Dextromethorphan (a synthetic analog of codeine and *d*-3-methoxy-17-methylmorphinan; Fig. 1) (DXM) is effective over the counter antitussive medicine widely used for treating chronic cough since the last four decades [1–3]. It brings relief from non-productive cough by directly acting on the cough centre present in the medulla [4]. Other uses of the drug include treatment of cold, pseudobulbar disorder, methotrexate-induced neurotoxicity, depression and pain relief [5–10]. Upon oral ingestion, dextromethorphan is quickly absorbed from the gastrointestinal tract and it starts exerting its activity within 15–60 min of ingestion [11,12]. The peak plasma concentration (in the range 1–20 μmol L^{-1}) is attained in almost 2–3 h [12]. DXM metabolises rapidly in liver to dextrorphan, 3-methoxymorphinan and 3-hydroxymorphinan and is mainly excreted as an unchanged parent drug and dextrorphan [13,14]. The drug is beneficial when administered in recommended doses. However, acute overdosage of DXM affects the central nervous system and may also lead to coma which can be fatal [15]. Administration of dextromethorphan with monoamine oxidase and selective serotonin re-uptake inhibitors is avoided because it may lead to accumulation of excess serotonin in the body causing serotonin syndrome, a life threatening condition [16,17]. Though DXM is a very effective safe-to-use medicament, a high dose of the drug replicates phencyclidine and alcohol like effect such as hallucination, paranoia, euphoria and suicidal tendency [18]. It is for this reason that the drug is massively abused worldwide for recreational purposes [19]. Popularly known as “skittles,” “robos,” “rojos,” “velvet,” “CCC” and “poor man's PCP” among recreational users, unrestricted access and low cost of the drug has made it an inexpensive alternative to illegal psychotropic drugs leading to a considerable increase in its abuse in recent years [20]. Frequent ingestion of extremely high doses of DXM has been reported to result in impaired motor function, increased heart rate and blood pressure, rhabdomyolysis and drug accumulation eventually leading to toxicity [21–23]. Hypoxic brain damage, though rare, may also occur [24]. According to the Drug Abuse Warning Network Report, almost 1% of all emergency room drug-related visits are related to DXM abuse [25].

Diphenhydramine, 2-(diphenylmethoxy)-*N*,*N*-dimethylamine (Fig. 1) (DPH), is widely used as an antiallergic, antiemetic and antitussive drug [26,27]. DPH can cause strong sedation and hence, is widely used for insomnia as well [28]. It is also used to manage drug-induced Parkinsonism [29]. Being an anticholinergic agent, it may cause side effects such as increased heart rate, dehydration, enlarged pupils, blurred vision, ringing in the ears and constipation [30]. Acute overdosage may lead to complications like kidney failure, pancreatitis, cardiac arrest, coma, or even death within 2–18 h [31–33]. The drug is widely distributed throughout the body and the peak plasma concentration is attained in about 2–3 h after dosage, with 5–15% of a therapeutic dose of the drug excreted unchanged in human urine [34,35]. Being easily available, DPH is sometimes used as a recreational drug due to its euphoria and delirium-induced hallucination properties, which can be fatal in case of serious overdose [36,37].

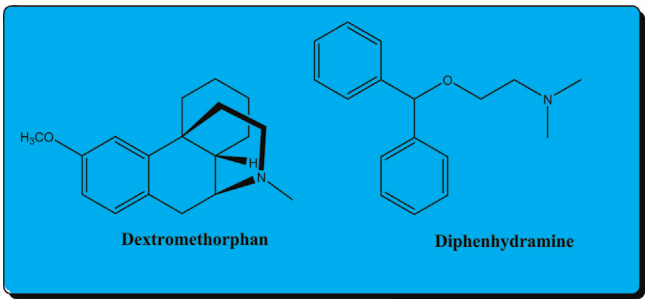

Fig. 1. Chemical structures of Dextromethorphan and Diphenhydramine.

On account of medical and pharmacological importance of DXM and DPH as well as the increasing trend of their abuse, there is a need to develop reliable, highly selective and sensitive analytical methods to quantify the drugs in pharmaceutical products and in human body fluids. An efficacious drug analysis requires achieving sensitivities at micromolar or even lower levels along with appreciable selectivity in real samples. Several analytical methods have been employed for the determination of the drugs. Most of these rely on chromatographic techniques such as high-performance liquid chromatography [38–41], gas chromatography [42–44] and thin-layer chromatography [45–47]. These methods require time-consuming sample preparation steps, expensive instruments and complex procedures. Currently, the area of development and application of electrochemical methods in pharmaceutical and biomedical analysis is under rapidly growing interest for the determination of extremely low concentration of drugs and/or their metabolites in clinical samples. The electroanalytical methods possess simplicity, high sensitivity, excellent selectivity, and low cost and are easy to use allowing direct analysis of analyte without the need of any separation or pre-treatment steps, thus making it an appealing method of choice for drug analysis [48]. The present paper aims to reveal the trends in the development of electrochemical methods for the determination of DXM and DPH to date. Various voltammetric and potentiometric methods used to determine the drug in bulk, pharmaceutical formulations and biological fluids have been discussed in the present review. To the best of our knowledge, this is the first attempt to summarise the electroanalytical methodologies reported for quantification of the over-the-counter non-narcotic antitussive drugs, DXM and DPH.

2. Electroanalytical methods

Electroanalytical methods belong to a group of techniques in analytical chemistry, wherein the analyte of interest is studied by measuring the voltage (potential) and/or current signals in an electrochemical cell. Their extensive use is attributed to relatively cheap instrumentation, high accuracy, precision and sensitivity, rapid analysis time, and ability to simultaneously determine various analytes in a solution [49]. Also, the technique boasts of direct analysis of the sample without any tedious and long preparative steps [50]. Hence, it is being increasingly used for drug analysis in pharmaceutical formulations and biological samples. There are a variety of electrochemical methods, the principal ones being voltammetry and potentiometry. The given review critically discusses the voltammetric and potentiometric methods reported in literature for the determination of the over-the-counter abused antitussive drugs, DXM and DPH.