Journal of Electroanalytical Chemistry 780 (2016) 153–159

Contents lists available at ScienceDirect

Journal of Electroanalytical Chemistry

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

Evaluation of taste masking effect of diclofenac using sweeteners and cyclodextrin by a potentiometric electronic tongue

Joanna Lenik [a,*], Małgorzata Wesoły [b], Patrycja Ciosek [b], Wojciech Wróblewski [b]

[a] Department of Analytical Chemistry and Instrumental Analysis, Faculty of Chemistry, Maria Curie-Skłodowska University, M. Curie-Skłodowska Sq. 3, 20-031 Lublin, Poland
[b] Department of Microbioanalytics, Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form 13 September 2016
Accepted 14 September 2016
Available online 15 September 2016

Keywords:
Electronic tongue
Ion-selective electrodes
Taste masking
Diclofenac

ABSTRACT

In this work a potentiometric electronic tongue based on classical ion-selective electrodes (6 types) and solid contact electrodes (2 types) was applied. The classical electrodes based on PVC membrane with other plasticizers exhibited cation-, anion-, amine-, and carbonate sensitivity, while the solid contact electrodes based on different lipophilic salts established diclofenac sensitivity. These sensors were used to assess the taste masking efficiency of diclofenac using selected sweeteners and cyclodextrin. Various amounts of four sweeteners (namely: sucrose, lactose, acesulfame K, sodium saccharin) as well as 2-hydroxypropyl-β-cyclodextrin were applied to mask the bitter taste of diclofenac. The signals of the sensor array registered during the experiments were processed by the Principal Component Analysis. The results obtained i.e. the chemical images of the samples indicated that the taste masking effect was the most pronounced for cyclodextrin, acesulfame K, sodium saccharin and for sucrose at higher concentration, whereas was almost negligible in the case of the presence of lactose in solution.

1. Introduction

The quality of medicinal products is an essential and significant problem worldwide. The drugs are subjected to quality control during their preparation with respect to the identity and purity as well as to the content of the Active Pharmaceutical Ingredient (API) [1]. Apart from the requirements for adult drugs (drug bioavailability, stability of the active substance), there are additional criteria for pediatric medicines such as the optimal form of the drug for the age group, the ease of administration for children, the acceptable taste of the oral drug and the safety of the applied excipients.

The barrier for the use of oral medications for children is the problem of taste masking of API. One of the requirements of the prescribed medicinal substances for children is the requirement of specified acceptable taste. This criterion refers to the drugs administered orally i.e. the substances in the aqueous solution, tablets for chewing, sucking, orally disintegrated tablets, pellets or syrups. Among many ways of taste masking the following can be included: addition of sweeteners and flavorings to the formula, coating of tablets with polymer films, microencapsulation, granulation [2,3]. Sweeteners are commonly used for the taste masking of pharmaceuticals in combination with other taste masking techniques. They can by mixed with bitter API for further coating or may be added to the coating liquid [4,5]. Since every sweetener exhibits different intensity of sweetness [6,7], it is difficult to correlate its chemical structure with taste and therefore elucidate the chemical mechanism of taste masking by sweeteners. Moreover, the taste masking efficiency of sweeteners depends on the applied API [8]. European Medicines Agency calls for restricting the use of artificial sweeteners (aspartame, sucrose), especially in medicines intended for children [9,10]. Moreover, other methods of taste masking are recommended due to allergic or toxic reactions and low effectiveness of sweeteners.

One alternative method is the complexation of the active substance with e.g. cyclodextrins (CD). Owing to their truncate cone structure, cyclodextrins have unique physicochemical properties and have the ability to selectively bind guest molecules forming stable 'host-guest' inclusion complexes, where the drug molecule fits wholly or partially into the cavity of the host molecule [11–12]. Since the cavity size of α-CD is insufficient for many drugs and γ-CD is expensive, β-CD was widely used in the early stages of pharmaceutical applications because of its availability and cavity size suitable for the widest range of drugs [13]. Usually the applied host/guest molar ratio is 1:1 and the taste masking is achieved by decreasing the oral solubility or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. Cyclodextrins were extensively tested for taste masking of bitter drugs [14]: 2-hydroxypropyl-β-cyclodextrin has been applied to mask the bitter taste of meloxicam [15], lidocaine hydrochloride [16]; β-cyclodextrin for taste masking of famotidine [17], cetirizine dihydrochloride [18], dextromethorphan hydrobromide, loperamide hydrochloride [19]; whereas α-,β-,γ-cyclodextrins for taste masking of hydroxyzine, cetirizine, and di-chlorpheniramine [20]. It should be also emphasized that many pharmaceutical products containing β-CDs are already commercially available, including non-steroidal anti-

* Corresponding author.
E-mail address: j.lenik@poczta.umcs.lublin.pl (J. Lenik).

http://dx.doi.org/10.1016/j.jelechem.2016.09.017
1572-6657/

inflammatory drugs (NSAIDs): indomethacin, piroxicam, meloxicam, nimesulide, tiaprofenic acid and diclofenac [21].

In general, the taste of medicinal products is assessed by human sensory panels. However, the human sense of taste is very complicated, it varies between individuals, depends on the health of members of a panel – therefore, its sensing remains subjective. Additionally, different sensitivities of taste sensing are observed in adults and children [22]. There are also ethical and safety problems due to toxicity of new active ingredients. On the other hand, the electronic tongue was proposed as an alternative method for taste prediction of pharmaceuticals. Electronic tongues (ETs) are systems composed of a set of non-selective sensors (a sensor array) and a data analysis system (pattern recognition system), allowing to extract the useful information from sensor responses. Such systems provide objective, automatic analysis of complex liquid samples, including the evaluation of taste of medicines [2,23–24]. Electrochemical and optical sensors as well as various biosensors are introduced in the sensors arrays of ETs [24] and can be applicable for potentiometric and voltammetric, determination of diclofenac in pharmaceuticals or biological samples [25,26]. However, potentiometric sensors – ion-selective electrodes based on polymeric membranes – are the most commonly applied due to their inherent advantages such as: low cost, simple design and construction, reasonable selectivity and sensitivity, fast response time [25,27].

Many architectures of potentiometric sensor arrays were proposed to evaluate the taste masking efficiency of medicines realized using different approaches. For example, the taste masking microencapsulation of Ibuprofen and Roxithromycin was detected by classical ion-selective electrodes coupled with Principal Component Analysis [28,29]. The encapsulation effect was proved after Eudragit modification of both APIs using the spray drying technique i.e. significant difference between chemical images of pure API and encapsulated API was noticed. Detailed studies were carried out to analyze the performances of potentiometric sensors working in various sensor array configuration (batch set-up, flow-through set-up and flow injection analysis set-up) for the classification of pure Ibuprofen and Ibuprofen modified with co-spray dried excipients (Eudragit E or Eudragit E with SLS) [30]. Similar automated electronic tongue with Sequential Injection Analysis (SIA) system was used for the simultaneous quantitative analysis of selected drugs such as: acetaminophen, ascorbic acid and acetylic acid in the presence of caffeine [31]. The suitability and comparison of two commercial electronic tongues systems (AlphaMOS electronic tongue Astree2 and Insent taste sensing system TS-5000Z) for the taste masking of various APIs (ibuprofen, quinine, cetirizine, loperamide, dextromethorphan, diclofenac) by maltodextrin and cyclodextrin complexation was reported [19,32,33]. In the next studies, AlphaMOS Astree2 system provided the evaluation of the taste masking effect of conventional pharmaceutical sweeteners [8], whereas the taste sensing system TS-5000Z was used to rationalize the development of oral taste masked diclofenac formulations [34]. Moreover, inter-laboratory studies were carried out to compare the performances of six different electronic tongues (two commercially available and four laboratory prototypes based on potentiometric and voltammetric sensors) for taste sensing of caffeine citrate solutions [35]. Finally, it should be also added that potentiometric sensor arrays were also utilized to assess the taste of pharmaceuticals (especially the bitter taste, see e.g. [36,37]).

The aim of the present paper was to study the efficiency of masking the bitter taste of diclofenac (a nonsteroidal anti-inflammatory drug applied to reduce inflammation, fever and pain) with various amounts of sweeteners and 2-hydroxypropyl-β-cyclodextrin using a potentiometric electronic tongue. The application-oriented sensor array was based on classical ion-selective electrodes of different selectivity and additional solid contact electrodes sensitive towards diclofenac.

2. Experimental

2.1. Chemicals and membrane materials

All used inorganic salts were of analytical grade. The active pharmaceutical ingredient diclofenac sodium salt (DICLO) as well as: sucrose, lactose, acesulfame K, sodium saccharin and 2-hydroxy-propyl-β-cyclodextrin (HPβCD) were purchased from Sigma-Aldrich. The components of the membranes: high-molecular weight poly(vinylchloride) (PVC); plasticizers: bis(2-ethylhexyl) sebacate (DOS), *o*-nitrophenyl octyl ether (*o*-NPOE); lipophilic salts: potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate (KTFPB), tridodecylmethylammonium chloride (TDMAC); ionophores: carbonate ionophore VII and calix[6]arene-hexaacetic acid hexaethylester (amine ionophore I) were purchased from Fluka. Additionally, lipophilic salts: methyltrioctylammonium chloride (Serva), tetraoctylammonium chloride (Fluka) and ionophore heptakis (2,3,6-tri-*O*-benzoyl)-β-cyclodextrin (HSBβCD, Sigma-Aldrich) were used in electrodes with solid contact.

2.2. Sensor array system and measurements

The classical electrodes were prepared according to early elaborated method [28], whereas the preparation of solid contact electrodes sensitive for diclofenac was presented in [38]. The components of the polymer membranes and composition of internal filling and conditioning solution as well as the composition of two layers phase of solid contact diclofenac electrodes were collected in Table 1.

The sensor array consisted of 16 ion-selective electrodes with plasticized PVC membranes of classical and solid contact architecture (two electrode specimens were prepared for each membrane composition, Table 1). The solid contact electrodes were selective for diclofenac (electrodes 1–4), whereas electrodes 5–12 exhibited generic cation- (CS) and anion-sensitivity (AS) depending on the electroactive additive used. Moreover, amine- (AM, electrodes 13–14) as well as carbonate-sensitive electrodes (CARB, electrodes 15–16) were included to provide additional sensors exhibiting a modified selectivity patterns, which differ from that obtained for classical AS electrodes. The ISEs were

Table 1
Components and solutions use for the preparation of ion-selective electrodes.
M-MTOA - methyltrioctylammonium chloride, T-TOA - tetraoctylammonium chloride, CS - cation sensitivity, AS - anion sensitivity, AM – amine, D-DOS, N-NPOE, CARB - carbonate, DICLO, KTFPB, TDMAC, HSBβCD, ETH, – - see Experimental part.

El. no	Electrode type	Ionophore (% wt.)	Lipophilic salt (% wt.)	Plasticizer (% wt.)	Internal phase/filling solution	Conditioning solution
1–2	DICLO-M	HSBβCD (1.2%)	MTOA-Cl (0.4%)	NPOE (65.6%)	PVC/NPOE	–
3–4	DICLO-T	HSBβCD (1.2%)	TOA-Cl (0.4%)	NPOE (65.6%)	PVC/NPOE	–
5–6	CS-D	–	KTFPB (1%)	DOS (66%)	0.01 M NaCl	0.001 M NaCl
7–8	CS-N	–	KTFPB (1%)	NPOE (66%)	0.01 M NaCl	0.001 M NaCl
9–10	AS-D	–	TDMAC (3.5%)	DOS (66%)	0.01 M NaCl	0.001 M NaCl
11–12	AS-N	–	TDMAC (3.5%)	NPOE (66%)	0.01 M NaCl	0.001 M NaCl
13–14	AM-D	Amine ionophore I (5%)	–	DOS (68%)	0.01 M KCl	0.001 M KCl
15–16	CARB-D	ETH 6010 (0.7%)	TDMAC (0.3%)	DOS (62%)	0.1 M NaH_2PO_4	0.01 M NaH_2PO_4
					0.1 M Na_2HPO_4	0.01 M Na_2HPO_4
					0.01 M NaCl	0.001 M NaCl