https://doi.org/10.31925/farmacia.2022.5.4 **ORIGINAL ARTICLE**

TESTING SUITABILITY OF SWEETENERS IN MASKING THE TASTE OF LEVOCETIRIZINE DIHYDROCHLORIDE USING THE ELECTRONIC TONGUE METHOD

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Abstract

Overcoming the bitter taste is a main problem in developing a pleasant product, especially for paediatric patients. According to our best knowledge, literature data does not provide testing suitability of sweeteners in masking the taste of levocetirizine dihydrochloride in gels. The present work focuses on the effect of three sweeteners (neotame, saccharin sodium and cyclohexyl sulfamate sodium) on masking the bitter taste of levocetirizine dihydrochloride in a mucoadhesive gel. The study shows not only the graphs of the formulation, active pharmaceutical ingredient (API) and placebo, but also the process of the bitter substance release from the gel as seen using the electronic tongue. In this work a potentiometric electronic tongue based on 16 ion-selective electrodes with solid contact based on silver chloride electrode was used. The principal component analysis (PCA) method was used to analyse the results statistically. Release tests were also performed. The collected samples were analysed using the reversed-phase HPLC to determine the levocetirizine dihydrochloride content in each of them. The formulations presented in the plot form compact clusters which proves the repeatability of the e-tongue responses. The electronic tongue release study suggests that all the sweeteners in the appropriate concentrations presented in this study could mask the bitter taste of levocetirizine dihydrochloride.

Rezumat

Mascarea gustului amar este o problemă principală în dezvoltarea unui produs plăcut, în special pentru pacienții pediatrici. Lucrarea de față se concentrează asupra efectului a trei îndulcitori (neotam, zaharină sodică și ciclohexil-sulfamat de sodiu) asupra mascării gustului amar al diclorhidratului de levocetirizină într-un gel mucoadeziv. Studiul prezintă rezultatele formulării ingredientului farmaceutic activ (API) și placebo, precum și procesul de eliberare a substanței amare din gel, folosind metoda limbii electronice potențiometrice. Această metodă folosește 16 electrozi ion-selectivi cu contact solid pe bază de electrod de clorură de argint. Evaluarea componentelor principale a fost utilizată pentru a analiza statistic rezultatele. Alături de testele de cedare, probele colectate au fost analizate folosind HPLC în fază inversă pentru a determina conținutul de diclorhidrat de levocetirizină în fiecare dintre ele. Formulările prezentate formează clustere compacte care demonstrează repetabilitatea răspunsurilor e-limbii. Studiul de eliberare electronică a limbii sugerează că toți îndulcitorii în concentrațiile adecvate prezentate în acest studiu ar putea masca gustul amar al diclorhidratului de levocetirizină.

Keywords: electronic tongue, levocetirizine dihydrochloride, taste-masking

Introduction

In recent years, there has been a great deal of advancement in technologies for creating patient-friendly drug forms. The solution to problems with swallowing solid forms of the drug is to produce, for example, orally disintegrating tablets [1], effervescent tablets [2], orodispersible films [6], or forms dedicated especially to children, such as jellies [21]. An equally important problem is the taste of the drug. The taste sensation is a sensory response resulting from the interaction of the substrate and the receptors in the taste buds. Ion channels, transmembrane transporters and receptors are mainly involved in the bitter taste transduction. Many studies indicate the participation of G protein and GPCRs (G protein coupled receptors) in its formation [29]. A feeling of bitterness in the mouth, usually caused by the active substance, is an undesirable characteristic for the patient.

There are many techniques for masking the bitter taste. One usually used in oral liquid dosage form is to add sugars or sweeteners. The use of sweeteners also allows the drug to be used by diabetics or other people avoiding sugar consumption. Another

method is the use of cyclodextrins, which form specific complexes with molecules of the bitter substance [23]. β-cyclodextrin and hydroxypropyl-cyclodextrin are particularly useful in masking the taste [18]. These compounds not only mask the bitter taste, but also contribute to the increase in the solubility of many sparingly soluble substances [19], belonging to BCS class II or IV (biopharmaceutical classification system). The other well-known methods of masking the taste also include coating the particles of the bitter substance [22], the use of ion exchange resins, the use of substances allowing to obtain higher viscosity, e.g. polymers affecting the rheological properties of the drug form [4] and the use of various salts as excipients [16].

The methods of assessing the masking of the bitter taste are mainly based on the use of a human panel and the electronic tongue. Research on the human panel is biased by the error of subjective perception of taste by different people. The ethical and legal aspects are also a significant obstacle here [9]. Conducting such a study is also more difficult when we create a paediatric form, which is associated with a higher risk of conducting research on children due to adverse drug reactions and moral or ethical aspects [10]. Regardless of the aforementioned obstacles, it is children who are often the target group for manufacturers trying to create a form with a friendly taste. Electronic tongue is designed to mimic what is happening in the process of taste transduction. It consists of an array of electrodes with different properties, characterized by partial or cross selectivity [27]. The interaction between molecules with a specific taste and sensors with specific properties leads to a change in the electrical potential. The values of the generated potentials are collected and analysed by appropriate computer software [24]. Sensors and membranes are made of different materials and used depending on the type of sample you want to test. Several types of the electronic tongue have been invented, based on various measurement techniques, such as spectroscopy, potentiometry and voltammetry, differing mainly in the type of membranes. Ion-selective electrodes used in the study measure the electrode potential in relation to the Ag/AgCl reference electrode [28].

The electronic tongue method is most often used in the food industry, e.g. for the analysis of honey, wine, coffee as well as the effects of mutual enhancement of flavour by various food ingredients. It is also important in determining the purity of water in rivers. In recent years, it has started to be used for pharmaceutical applications. The effect of selected sweeteners on masking the taste of paracetamol, ibuprofen, tramadol and sildenafil [7] and the effect of sweeteners and cyclodextrins on masking the taste of diclofenac [12] have already been investigated. Various drug forms were tested using the electronic tongue, e.g. microspheres [26], polymer-coated API particles, ODTs (orally disintegrating tablets), ODFs (orally disintegrating films) [30], suspensions, liquids [3, 20, 39], syrups.

In our work, we investigated the effect of three sweeteners on masking the bitter taste of levocetirizine dihydrochloride in a mucoadhesive gel. The developed gel is going to be used for the production of oral films using the 3D printing technique. Unfortunately, tests with prepared oral films were unsuccessful because oral films were clogging the electrodes with polymer membranes. Thin orodispersible films turn into gel within seconds after contact with moisture. Because of that, there is an expectation that the gel is going to taste the same as the oral films prepared from this gel. Levocetirizine dihydrochloride is a frequently used drug belonging to the group of second-generation anti-histamine drugs. Because of that, it is the drug of choice for many anti-allergic indications. It is often used in paediatric formulations such as solutions or oral drops. Levocetirizine dihydrochloride is characterized by an unpleasant bitter taste, as confirmed by literature. Because of that, the drug is a good candidate for taste masking. Formulating taste-masked oral films with levocetirizine dihydrochloride allows to enhance the mouthfeel and convenience of paediatric patients.

Food approved sweeteners were used.

Neotame – a derivative of aspartame, but approx. 30-60 times sweeter than it. It is 6,000-10,000 times sweeter than the commonly known sucrose, which allows it to be used in very small amounts. It has a good flavour profile [17].

Sodium saccharin – 300 - 500 times sweeter than sucrose. Sensitive to high temperature. It has a slight metallic aftertaste [5, 28].

Cyclohexyl sulfamate sodium – a non-toxic sweetener with a sweetening power lower than that of sodium saccharin, but insensitive to high temperatures [20].

The study shows not only the graphs of the formulation, API and placebo, but also the process of the bitter substance release from the gel as seen using the electronic tongue.

Materials and Methods

Materials

Levocetirizine dihydrochloride was obtained from Dr. Reddys (Hyderabad, India). Manucol (Sodium alginate) (65 mPas, 1% in H_2O at 20°C) was kindly donated by FMC BioPolymer (Philadelphia, USA). Glycerol 85% pharmaceutical grade was purchased

from Coel Laboratory Pharmaceuticals (Kraków, Poland). Mowiol, (Poly(vinyl) alcohol - PVA), 98 - 98.8% hydrolysed, M.V. approx. 31000 - 50000 (5.4 - 6.5 mPas, 4% in H_2O at 20°C) and saccharin sodium salt were purchased from ACROS ORGANICS (Geel, Belgium). Neotame was purchased from Corbosynth Limited (Compton, Great Britain). Cyclohexyl sulfamate sodium was purchased from Sigma Aldrich (St. Louis, USA). Distilled water was obtained by laboratory distillation of demineralized water.

The components of the membrane such as the polymer poly(vinylchloride) (PVC) was from (Tarwinyl Tarnów Poland); 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) were from Fluka, St. Gallen, Switzerland, tetradodecylammonium tetrakis(4-chlorophenyl)borate (TDATPCB) was from Sigma Aldrich (St. Louis, USA). Ionophores such as: carbonate ionophore VII, ETH 6010 was from Fluka St. Gallen, Switzerland, 3-mercapto-5-/2'-hydroxynaphthyl-azo-triazole (METRIAN) was from Department of Drug Chemistry, Medical University of Lublin, Poland).

All used inorganic salts were of analytical grade. All aqueous solutions were prepared with deionized water of conductivity 0.07 μS/cm (Elix Advantage System Mili-Q plus Milipore, Spittal an der Drau, Austria).

Formulations and preparation of gels

The quantitative and qualitative compositions of the formulations are presented in Table I. The concentrations of sweeteners were selected based on the literature data in such a way as to achieve the optimal sweetening effect with their minimal participation in the formulation.

The first step was to make a PVA gel. A gel with a concentration of 20% was prepared in each case. For this purpose, 4 g of PVA and 16 g of water were weighed. Both components were transferred to a beaker and placed on the heating plate. The heater was set to 70°C. The components were mixed with a mechanical stirrer until the PVA was completely dissolved (about 2 hours). Finally, water losses were replaced.

The second step was to prepare a 5% manucol auxiliary gel. For this purpose, 5 g of polymer and 95 g of water were weighed. The components were also transferred to a beaker and placed on the heater. The suspension was stirred until manucol was completely dissolved at 60°C (about 1 hour). After dissolution, the mixture was made up with water and mixed again.

In the next step, an auxiliary solution of the active substance was prepared. 3 g of levocetirizine dihydrochloride was dissolved in a 100 mL flask, making up to the mark with water and thoroughly mixing the solution until dissolved.

Depending on the formulation, the following auxiliary sweetener solutions were added to the gel.

Formulations 1 and 2 – neotame. An auxiliary solution of 40 mg neotame in 10 mL of water was prepared. 1 mL of the solution was pipetted to prepare both formulations.

Formulations 3 and 4 – sodium saccharin. 150 mg of sodium saccharin was dissolved in 5 mL of water and added to both formulations.

Formulations 5 and 6 – cyclohexyl sulfamate sodium. An auxiliary solution of 850 mg of cyclohexyl sulfamate sodium in 10 mL of water was prepared. 1 mL of the solution was withdrawn with the calibration pipette to prepare both formulations.

The mentioned formulation components were combined in a beaker at room temperature by mixing on a mechanical stirrer. The compositions of all formulations are presented in Table I.

Table I

The weight (g) of ingredients in formulations of tested gels

Formulation	1	2	3	4	5	6
Levocetirizine dihydrochloride	-	0.150	-	0.150	-	0.150
Mowiol	4.0	4.0	4.0	4.0	4.0	4.0
Manucol	0.86	0.86	0.86	0.86	0.86	0.86
Glycerol	1.5	1.5	1.5	1.5	1.5	1.5
Neotame	0.004	0.004	-	-	-	-
Saccharin sodium	-	-	0.15	0.15	-	-
Cyclohexyl sulfamate sodium	-	-	-	-	0.085	0.085
Water	ad 50.0	ad 50.0	ad 50.0	ad 50.0	ad 50.0	ad 50.0

Dissolution tests

The release tests of three gels (formulations 2, 4, 6 from Table I) were carried out in purified water in 100 mL vessels (Erweka DT600, Heusenstamm, Germany). The water temperature was 37°C. A paddle apparatus was used, and the rotation speed of the stirrer was 100 rpm. Gel with a concentration of 3.0 mg/g of levocetirizine dihydrochloride was introduced to the bottom of the vessel using a syringe with a capacity of 10 mL tubing in a mass

of 6 g. The syringe was fitted with a polyethylene tube of internal/external diameter of 3.73/4.88 mm. The tube was long enough to reach the bottom of the vessel. The gel was extruded using the graduation on the syringe. However, each time it was controlled using balance if the exact amount of gel was extruded. 1 mL of dissolution medium was collected every 1, 3, 5, 8 minutes, then losses were made up.

The collected samples were analysed using the reversed-phase HPLC (high-performance liquid chromatography) (Shimadzu Corporation, Kyoto, Japan) to determine the levocetirizine dihydrochloride content in each of them. A liquid chromatograph equipped with a UV diode detector was used for determinations. A column (RP18) with parameters 4.6 mm x 150 mm was used. The oven temperature was 25°C. The mobile phase used was a mixture of phosphate buffer pH 3.0 and acetonitrile in the proportions 65:35 (v/v), and flow 1 mL/min (isocratic method). The injection volume was 15 µL. Retention time was about 7 minutes.

Preparation of the electronic tongue sensor matrix and potentiometric measurements

The sensor matrix consisted of 16 ion-selective electrodes with solid contact based on silver chloride electrode. The design of the electrodes and preparation of the membrane were described in an earlier work [25]. The tests used sensors with different selectivity for carbonate and zinc ions, as well as cation-selective (CAT) and anion-selective (AN) electrodes, and cation-anion selective (CAT-AN) with mixed selectivity in order to increase the multi-functionality of the device. The membranes of the cation-selective electrodes contained 1% (w/w) lipophilic KTFPB salt, 66% (w/w) plasticizer and 33% (w/w) poly(vinyl chloride). The membranes of the anion-selective electrodes contained 3.5% (w/w) TDMAC lipophilic salt, 64% (w/w) plasticizer and 32.5% (w/w) PVC. The mixed selectivity electrode membrane consisted of 3% (w/w) TDATPCB salt, 65% (w/w) plasticizer and 32% (w/w) PVC. The electrode sensitive to zinc ions contained 4% (w/w) METRIAN ionophore, 66% (w/w) NPOE plasticizer and 30% (w/w) PVC. The carbonate electrode contained the ionophore ETH 6010 (0.7% w/w), TDMAC (0.3% w/w), DOS (62% w/w) and PVC (37% w/w). Two sensors were prepared for each membrane composition. The qualitative composition of membranes for individual sensors is presented in Table II.

Table II

Membrane composition of ion-selective electrodes included in the sensor matrix of ET (electronic tongue)

Electrode number	Electrode type	Ion exchanger	Ionophore	Plasticizer
1-2	CAT-D	KTFPB	-	DOS
3-4	CAT-N	KTFPB	-	NPOE
5-6	AN-D	TDMAC	-	DOS
7-8	AN-N	TDMAC	-	NPOE
9-10	CAT-AN -D	TDATPCB	-	DOS
11-12	CAT-AN-N	TDATPCB	-	NPOE
13-14	Zn^{2+}-N	-	METRIAN	NPOE
15-16	CO_3^{2-} D	TDMAC	ETH 6010	DOS

Immediately after preparing the electrodes, the sensors were conditioned with constant stirring for 24 hours in the appropriate solutions. The cation-, anion- and cation-anion selective electrodes (No. 1-12) were conditioned in a NaCl solution with a concentration of 10^{-3}M. Zinc electrodes (No. 13-14) were conditioned in a $ZnCl_2$ solution with a concentration of 10^{-3}M, carbonate electrodes (No. 15-16) were conditioned in a solution of NaH_2PO_4 (0.01M) + Na_2HPO_4 (0.01M) + NaCl (0.001M).

The electrodes were kept in the air between the measurements.

All potentiometric measurements were performed in a measuring cell having the following scheme: Ag, AgCl; KCl 3M $\vert$ CH_3COOLi 1M $\vert$ sample solution $\Vert$ membrane $\Vert$ PVC+plasticizer (solid contact); AgCl, Ag. The measurements of the electromotive force of the system ion-selective electrodes - reference electrode (Orion 90-02) - were carried out using Electrochemistry EMF Interface system (Lawson Labs. Inc., Malvern, USA) and IBM PC computer.

Before measuring pharmaceutical samples, the potentiometric sensors were calibrated several times according to a specific procedure in order to obtain and ensure the correct response of the electrodes. For this purpose, calibration curves of the developed sensors were determined in solutions of levocetirizine dihydrochloride (CET) in the concentration range 10^{-5} - 10^{-2} M. Before calibration, the electrodes were conditioned for 15 minutes in a 10^{-3} M CET solution. Based on the determined calibration curves, the slope coefficient was determined, as well as the correlation coefficient of the linear regression curve to the measurement points.

Measurements of pharmaceutical samples in the form of gels with the ET were performed as follows. Ion-selective electrodes (16 sensors) were immersed in 50 mL deionized water for 5 minutes

to stabilize the signal. Then, 3 mL of the appropriate gel (Formulations 1 - 6, Table I) was added with a syringe to the same water sample. Measurement of the electrode potential change was recorded for the next 10 minutes. The samples were mixed with a magnetic stirrer. The release measurements were performed for pure API (CET) solutions, and for all tested API formulations (no 2, 4, 6, Table I) and corresponding placebo (no 1, 3, 5, Table I). Sensor signals were recorded for 15 min in 5 replicates for each sample type. The sensors were rinsed with water and then blotted dry between tests.

Results and Discussion

Characteristics of the electrodes

As a result of the calibration of ion-selective electrodes, appropriate calibration curves were obtained. The measurement results are presented in Table III.

Depending on the active substance used in the polymer membrane, the sensors have a cationic function (electrode types CAT-D, CAT-N, CAT-AN-D, CAT-AN-N, Zn^{2+}-N) and anionic function (electrode types AN-D, AN-N, CO_3^{2-}-D). For all electrodes with an ion exchanger, relatively better parameters were observed for membranes plasticized with polar o-nitrophenyl octyl ether than with lipophilic bis (2-ethylhexyl) sebacate. The characteristic slope most similar to the theoretical one is shown by the electrode with the cation-anion exchanger dissolved in NPOE (CAT-AN-N). The electrodes containing quaternary ammonium salt and electrodes selective for zinc and carbonate ions are less sensitive. The electrodes containing the tetraphenylborate derivative as the active substance are characterized by super-Nernstian response. Diversified, high sensitivity of the electrodes may indicate the possibility of their application to a potentiometric sensor array used for the chemometric analysis of pharmaceutical samples containing levocetirizine dihydrochloride.

Table III

Characteristics of sensors included in the matrix of electronic tongue

Type of electrode	Sensitivity (mV/dec)	Linear range (M)	R^2	n
CAT-D	77.46 ± 5.87	$10^{-5} – 10^{-3}$	0.9897 ± 0.0263	5
CAT-N	85.86 ± 9.33	$10^{-5} – 10^{-2}$	0.9947 ± 0.0013	5
AN-D	-48.60 ± 4.59	$10^{-5} – 10^{-3}$	0.9749 ± 0.0397	3
AN-N	-26.42 ± 2.33	$10^{-5} – 10^{-2}$	0.9905 ± 0.0036	3
CAT-AN -D	49.29 ± 12.22	$10^{-5} – 10^{-3}$	0.9777 ± 0.0166	3
CAT-AN-N	60.04 ± 3.58	$10^{-5} – 10^{-2}$	0.9908 ± 0.0115	5
Zn^{2+}-N	28.88 ± 22.50	$10^{-5} – 10^{-3}$	0.9613 ± 0.0048	3
CO_3^{2-} D	-34.33 ± 11.74	$10^{-4} – 10^{-2}$	0.9662 ± 0.0157	3

±SD (standard deviation)

Dissolution tests of gels with levocetirizine dihydrochloride

A dissolution test was performed to correlate the results from the electronic tongue. The gels were tested two days after being performed in a paddle apparatus (Ph.Eur.). Release from all samples occurred at a similar rate. After 8 min the release from the formulation containing neotame was 31%, while for formulations 4 and 6 it reached 26%. Dissolution profiles are presented in Figure 1. All tests were repeated in triplicate.

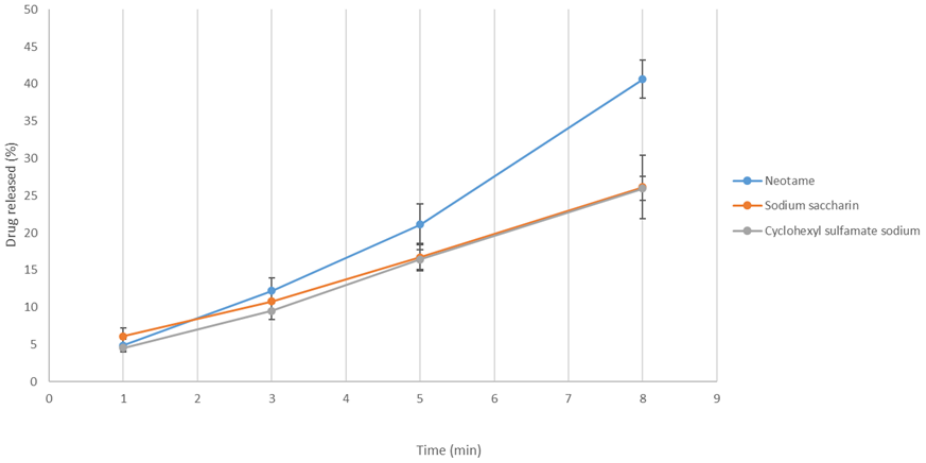

Figure 1.

Dissolution profiles of the three gels

Results of electronic tongue measurements

Sample testing with the electronic tongue was performed for all formulations mentioned (1 - 6) and for pure API in order to compare API taste, API formulation and placebo formulation. The test results are presented in Figures 2, 3, 4 and 5.

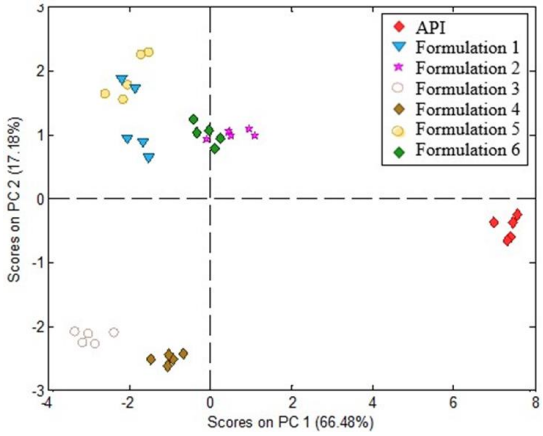

Figure 2.

PCA score plot of all formulations (2 minutes after the start of release)

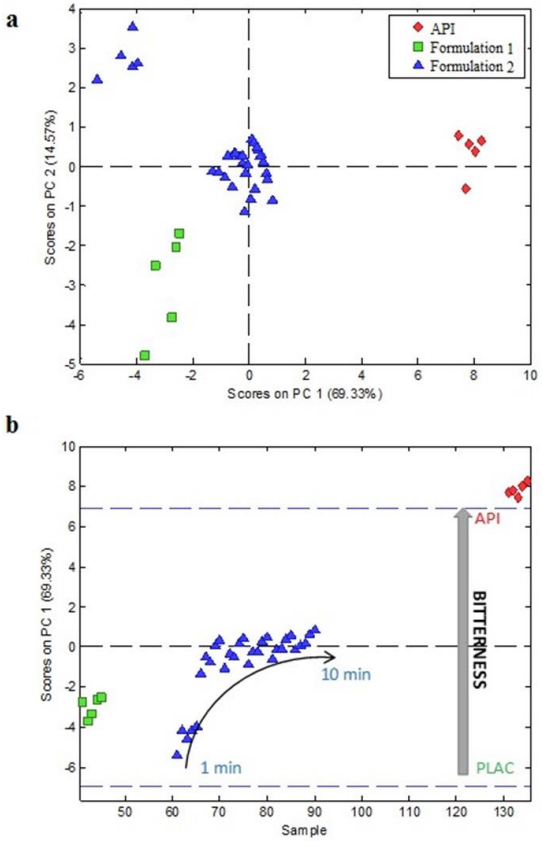

Figure 3.

PCA plot for the results of electronic tongue measurement: a) clusters of formulations 1 and 2 and API in the PC1-PC2 coordinates; b) change of the first principal component in 0 - 10 min for formulation 2 showing release of API

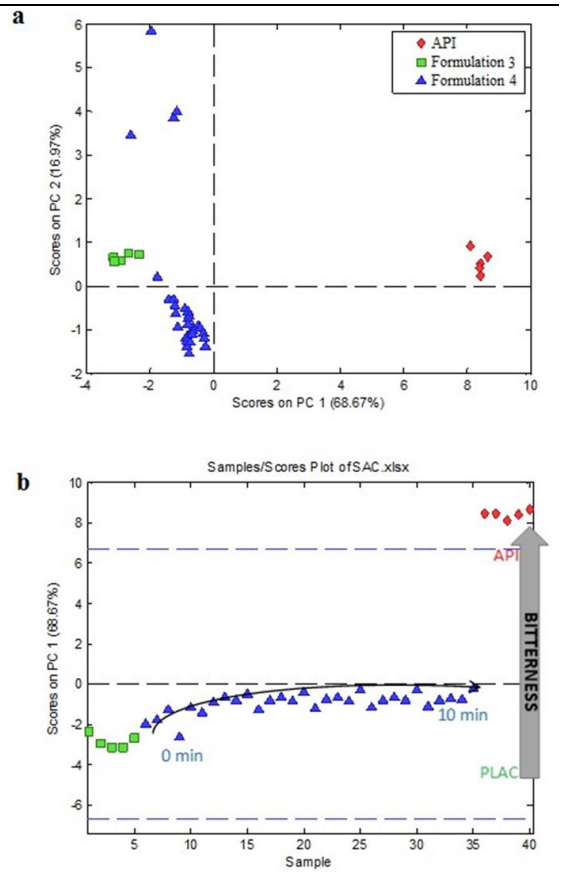

Figure 4.

PCA plot for the results of electronic tongue measurement: a) clusters of formulations 3 and 4 and API in the PC1-PC2 coordinates; b) change of the first principal component in 0 - 10 min for formulation 4 showing release of API

Levocetirizine dihydrochloride has been described in several approaches as a bitter taste drug. There are a lot of methods of taste masking of drugs including film coating, complexation with resins or cyclodextrins, using sweeteners, etc. Several authors used the drug complexation method to overcome the unpleasant taste of levocetirizine dihydrochloride. Taste masking effectiveness was assessed using human volunteers. It was confirmed, that the applied method was effective in taste masking and increased patients acceptance [14, 34]. In another study, cetirizine-based microspheres were examined using an electronic tongue. Film coating of microspheres was evaluated as a method of taste masking. It was proven that taste masking efficiency relied on the type of microencapsulating polymer used and the ratio of API to polymer [26]. Mahesh *et al*. developed fast disintegrating films of levocetirizine dihydrochloride for oral use. The authors used cyclodextrins in combination with sweeteners (aspartame and sucralose). However, attempts to mask unpleasant taste using sweeteners alone without cyclodextrins were not successful [15].

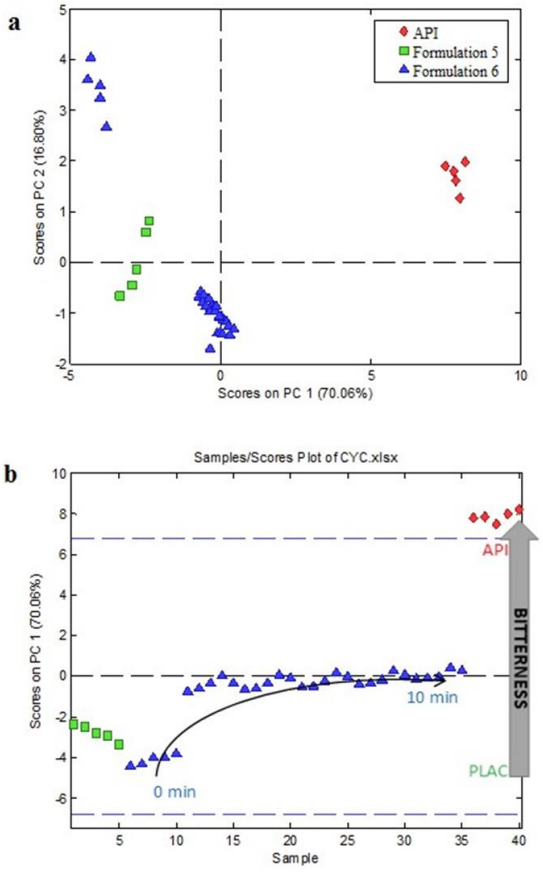

Figure 5.
PCA plot for the results of electronic tongue measurement: a) clusters of formulations 5 and 6 and API in the PC1-PC2 coordinates; b) change of the first principal component in 0 - 10 min for formulation 6 showing release of API 6

Choudhary *et al*. developed a quick-dissolving film of levocetirizine dihydrochloride, where neotame with citric acid were employed to mask the bitter taste of levocetirizine dihydrochloride [8]. According to our best knowledge, literature data does not provide test suitability of sweeteners like sodium saccharin, and cyclohexyl sulfamate sodium in masking the taste of levocetirizine dihydrochloride. In our study, an electronic tongue was used to compare the effectiveness in taste-masking properties of three selected sweeteners – neotame, sodium saccharin, and cyclohexyl sulfamate sodium. The applied method allowed to avoid using a human taste panel.

The low selectivity of the sensors results in obtaining a large amount of information from the samples. Sometimes the data from one sensor can be misleading, e.g. if it is more selective for the taste masking substance than for the active substance. Multidimensionality of the obtained data requires the use of statistical methods allowing for their reduction, ordering and thus creating a clear image of the taste. The most commonly used method is MVDA (multivariate data analysis) or PARC (pattern recognition). In our study, we used a method based on MVDA, or more precisely PCA (principal components analysis), the purpose of which is to show a specific direction of data variability and arrange them in space. In this method, reduced variables are usually shown in the form of a two-dimensional map. The x-axis is usually PC-1, which brings together more information and the y-axis is PC-2, which contains less statistically significant information [11]. Principal components scores are linear combinations of responses of all sensors present in the array and when presented in PCA plot they show the similarity of chemical images of the analysed samples. Change of position of sample chemical image on PCA plot is evidence of the change of its properties, like release degree or bitterness [13].

The PCA method was used to analyse the results statistically. The formulations presented in the plot form compact clusters (which proves the repeatability of the e-tongue responses), which generally do not overlap in the PC1-PC2 space (Figure 2) All three sweeteners discussed in the study (neotame, sodium saccharin, and cyclamate) seem to mask the taste to a similar degree. Each time PC1 values for formulations with API and a sweetener comes closest to the value corresponding to the pure sweetener (Figure 2). Moreover, in the PCA plot, the distances between the API and formulations 2, 4, 6 (levocetirizine dihydrochloride formulations) are substantially greater than between the API and respective placebo formulations. This allows the conclusion that the bitter taste of the active substance is effectively masked by all three sweeteners. The main sources of variability were studied by looking at loadings of the first PCs in Figure 2. For PC1, the most meaningful responses were observed in the case of CAT-D, CAT-N, CAT-AN-D, Zn^{2+}-N, and CO32—D electrodes, whereas for PC2 in the case of AN-N and CAT-AN-N electrodes. It is in good agreement with our previous findings considering the sensitivity of CAT-N, CAT-D, and AN-N electrodes towards cetirizine HCl [26].

To investigate the effect of the sweeteners in masking the taste of levocetirizine dihydrochloride in more detail, each of them was analysed separately. The first figure (a) for each of the presented formulations (Figures 3-5) show a graph according to the PC1-PC2 coordinates. Each of the presented graphs shows the separation of a group of substances. Similar to Figure 2, the placebo formulation, API and the API formulation are linearly separable. The analysis of PC1 values shows that there are no significant differences between the sweeteners when analysed separately, and the groups they form in the plot are similar to

placebo to a much greater extent than to API, which indicates masking the taste of API. The analysis of the PC2 axis values shows that the greatest differences in values between API and the formulation with a sweetener and API were found for sodium cyclamate. Smaller differences are seen for sodium saccharin. The worst results on the PC2 scale were obtained for neotame.

The second graph (b) in Figures 3, 4, and 5 shows how the chemical image of the tested samples changes only along the PC1 axis, describing in each case (Figures 3a, 4a, 5a) about 70% of the variability contained in the original data set consisting signals obtained for API, the tested formulation with API, and a corresponding placebo. For comparison, the variability of the PC2 axis is about 17%. In any case, the placebo formulation is low along the PC1 axis, and pure API is the highest, so as PC1 increases, a change in "bitterness" of the test samples can be described. The formulation with API and sweetener is in between, but closer to placebo, which confirms the intermediate characteristics of the tested formulations in comparison with the bitter API and the non-bitter placebo. At zero minute of measurement, formulations 2, 4 and 6 are very close to the PC1 values shown by the corresponding placebo. Over time, PC1 values increase slightly, up to 10 minutes, when they stabilize, stopping between API and placebo. The stabilization of the PC1 value allows the conclusion that the presented sweeteners are able to mask the bitter taste of levocetirizine dihydrochloride during the slow dissolution of the gel.

Conclusions

The electronic tongue is one of the objective methods of testing the taste masking of bitter active substances. This method can be a tool for evaluating a pharmaceutical formulation complementary to traditional methods. The human panel is the most reliable and frequently used technique, but it has some limitations related to drug toxicity and the dangers of drug testing in humans. Especially considering the research in children, it may not be possible to carry out. For these reasons, the use of the electronic tongue as a method of testing taste is perfectly justified.

The conducted analysis showed the usefulness of three sweeteners, such as neotame, sodium saccharin and cyclamate, in terms of masking the bitter taste of levocetirizine dihydrochloride. The electronic tongue release study suggests how bitterness has changed with the increase in drug concentration in the dissolution medium. Stabilization of the value on the PC1 scale for 10 minutes indicates that during the gradual release of API from the gel, all the sweeteners in the appropriate concentrations presented in this study seem to be able to mask the bitter taste of API.

Conflict of interest

The authors declare no conflict of interest.

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