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Short communication

Following drug degradation and consequent taste deterioration of an oral reconstituted paediatric suspension during dosing interval via electronic tongue

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ABSTRACT

Background: The taste of oral liquid dosage forms is a crucial factor that impacts pediatric patient compliance. Taste of suspensions can be typically evaluated by human volunteers. Recently, the electronic tongue (ET) has been proven as an emerging tool that could be useful to follow up various formulations' properties like taste and composition. This study aimed to evaluate the potential use of ET in assessing the taste deterioration of reconstituted oral suspensions and compare the results obtained with the typical in vivo panel taste method.

Methods: Four commercially available brands of amoxicillin/ clavulanic acid suspensions (one brand and three generic formulations) were reconstituted and stored in refrigerator to assess their taste on a daily basis. The taste of these products was assessed using Alpha-Astree ET and the obtained results were compared with those obtained from an in vivo panel taste assessment using a hedonic panel test (the 5-point hedonic scale).

Results: All evaluated suspensions exhibited similar trends. ET and in vivo analysis indicated low taste scores for all evaluated suspensions immediately after reconstitution, possibly due to the incomplete dissolution of sucrose. The scores for all formulations were higher on day 2, followed by a steady state for the next two days. After that, a significant decay in the scores was observed in the fifth day for all evaluated suspensions. ET results were in excellent agreement with the results obtained via in vivo panel test method.

Conclusion: The ET seems to be promising for testing the taste of pharmaceutical liquid preparations and evaluate possible deterioration upon storage or after reconstitution. It may provide a platform to avoid the involvement of pediatric volunteers in clinical evaluation and can be employed as a quality control tool during manufacturing.

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1. Introduction

Organoleptic properties, especially taste, are considered as a challenge during the development of oral liquid dosage forms. They are strongly related to patient compliance, which consequently may affect the therapeutic effectiveness (Enrica Menditto, Valentina Orlando et al. 2020). Thus, taste masking and taste evaluation have witnessed increasing attention from both industries and regulatory authorities. Traditional assessment of the taste of a pharmaceutical product is usually conducted on human volunteers, which is costly, time-consuming and sometimes harmful (Committee for Medicinal Products for Human Use

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(CHMP) 2013). Accordingly, reliable and predictive in vitro methods have been developed to assess the taste of pharmaceutical products (Hilton and Thomas, 2003, Khan, Khar et al., 2016, Mohamed-Ahmed, Soto J et al., 2016, Zontov, Balyklova et al. 2016). One of the newly used methods is the electronic tongue (ET), which is a multi-sensor system composed of a number of low-selective and cross-sensitive sensors, and uses advanced mathematical algorithms for signal processing based on multivariate analysis, e.g., pattern recognition (PARC) and artificial neural networks (ANNs) (Vlasov, Legin et al, 2005, Gebicki 2016, Mendez and Preedy, 2016).

ET is a robust tool that provides a fast and reliable detection of compounds in the liquids (Smyth and Cozzolino, 2012, Del Valle, 2017). ET has been used in many fields such as food industry, environmental, biotechnology, and most importantly oral pharmaceutical product evaluations (Legin, Rudnitskaya et al., 2004, Abu-Khalaf and Iversen, 2007). Recently, we have shown that ET can be employed successfully to assess the stability of Cefdinir suspension after reconstitution (Abu-Khalaf, Zaid et al., 2019). Eckert et al used ET as an alternative method in quality control of herbal lozenges. Moreover, superior sensitivity for the ET method compared to the human taste assessment was reported (Eckert, Lutz et al., 2011).

Amoxicillin/clavulanic acid suspensions are widely prescribed for infants and children. However, the two active pharmaceutical ingredients exhibit a very strong bitter taste and thus a large amount of sucrose is typical in these formulations. This report describes ET analysis of taste deterioration for four Amoxicillin/clavulanic acid suspensions after reconstitution throughout the duration of use., in addition to in-parallel clinical evaluation using a hedonic panel test.

2. Methods

Four different products of amoxicillin/clavulanic acid suspensions (400 mg and 57 mg, respectively per 5 mL) were purchased from a community pharmacy and evaluated for taste deterioration over time. These products were: Ogmin[®], Clamoxin[®], Moclav[®] and Augmentin[®].

An ET device (Alpha-Astree, Alpha MOS, Toulouse, France) was used for the taste assessment. It has seven sensors, and measurements are based on the potentiometric principle.

Prior to any analysis, the seven sensors of the ET went through a conditioning, calibration, and diagnostic process according to the manufacturer’s recommendation. Cleaning of the sensor array was carried out between each measurement using pure distilled water (Alpha MOS, 2009). In addition, data reduction (i.e. scaling and normalization) was conducted before the principal component analysis (PCA) was performed. Three samples of each antibiotic formula were re-suspended in 60 mL distilled water to yield a similar concentration of 400 mg/5 mL. Each sample was measured in triplicate. Data acquisition and data processing were achieved by the Alpha Soft software, while multivariate data analysis was used to analyse data. Prior to any measurement, a short run with three different concentrations (low, medium and high) of the reconstituted suspension was performed for the conditioning of the sensors. This fast-preliminary test confirmed the sensitivity of the sensors toward the tested products and their tested concentrations. Then, the same testing procedure was used over a period of one week to mimic the actual use.

PCA is a well-known multivariate data analysis technique, and it shows the variations of the measurements. It was used in several



Fig. 1. The Five Point Hedonic Scale.

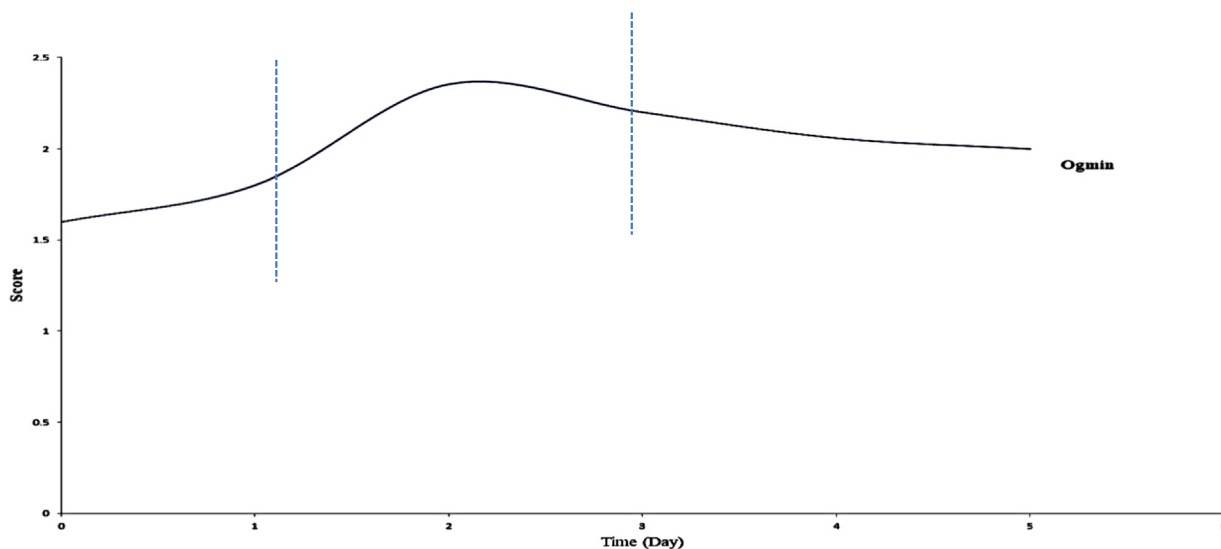


Fig. 2. (A): In-vivo test for Ogmin showing the mean response to the 5-point hedonic scale versus time. (B): PCA scores plot from the electronic tongue for Ogmin during testing days.

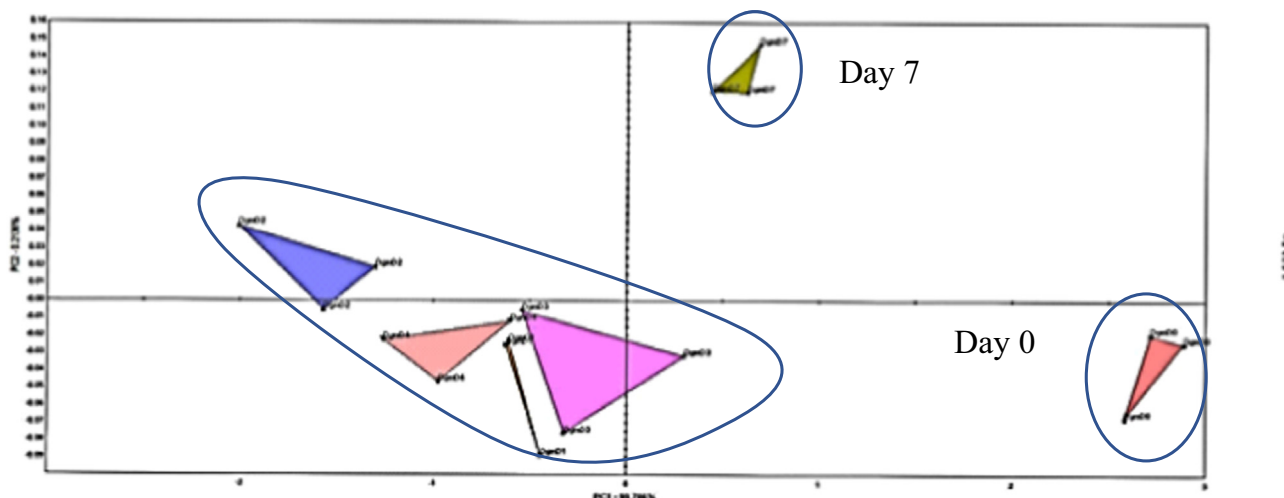


Fig. 2 (continued)

studies related to ET (Abu-Khalaf, Zaid et al., 2019, Al Ramahi, Zaid et al., 2019).

This study was conducted in accordance with the good clinical practice (GCP) guidelines and approved by the Institutional Review Board (IRB) of An-Najah National University.

Pediatric patients aged 3–12 years who were prescribed one of the commercial antibiotic suspensions included for any reason and who did not have an allergy to any of the products' ingredients were enrolled in this study. The nature and the importance of this study were explained to the parents, who approved the enrolment of their children in the study. After having their consent, the parents were asked to follow their children daily and ask them to sign one of the facial expressions according to the panel test shown in Fig. 1 on days 0, 1, 2, 3, 4 and 5 after the reconstitution.

The taste of all products was evaluated in the same manner. A teaspoonful of the prescribed antibiotic suspension was precisely administered to each pediatric patient who was then asked to immediately report his/her perception of the taste using the 5-point hedonic scale (scale: 1- extremely dislike; 2- slightly dislike;

3- neither like nor dislike; 4- slightly like; 5- extremely like), where one indicates a very sad and unacceptable taste, while five indicates a happy face due to the good taste of the product (Fig. 1).

The points from the children's responses were reported by their parents, then the mean was calculated for each product and the mean response time was plotted for each product.

3. Results

Four antibiotic products of amoxicillin/ clavulanic acid were evaluated, a clear agreement between in vivo and in vitro assessment was found as shown in Figs. 2-5.

The in vivo part included 64 volunteers, who were prescribed one of the four evaluated formulations, among them 37 (57.8%) were males, their age ranged from 3 to 12 years with a mean age \pm SD of 8.21 ± 2.58 years. The mean of scored values for the four formulations were plotted as a function of time as shown in Figs. 2-5 (A). It can be noticed that in-vivo scales (for each medi-

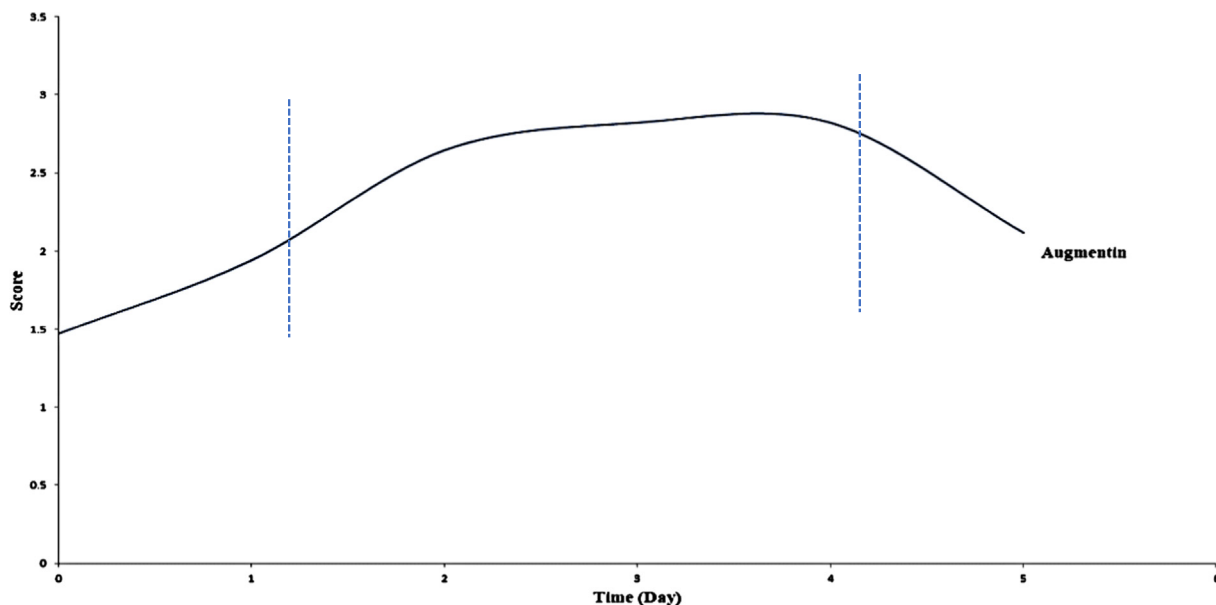


Fig. 3. (A): In-vivo test for Augmentin showing the mean response to the 5-point hedonic scale versus time. (B): PCA scores plot from the electronic tongue for Augmentin.

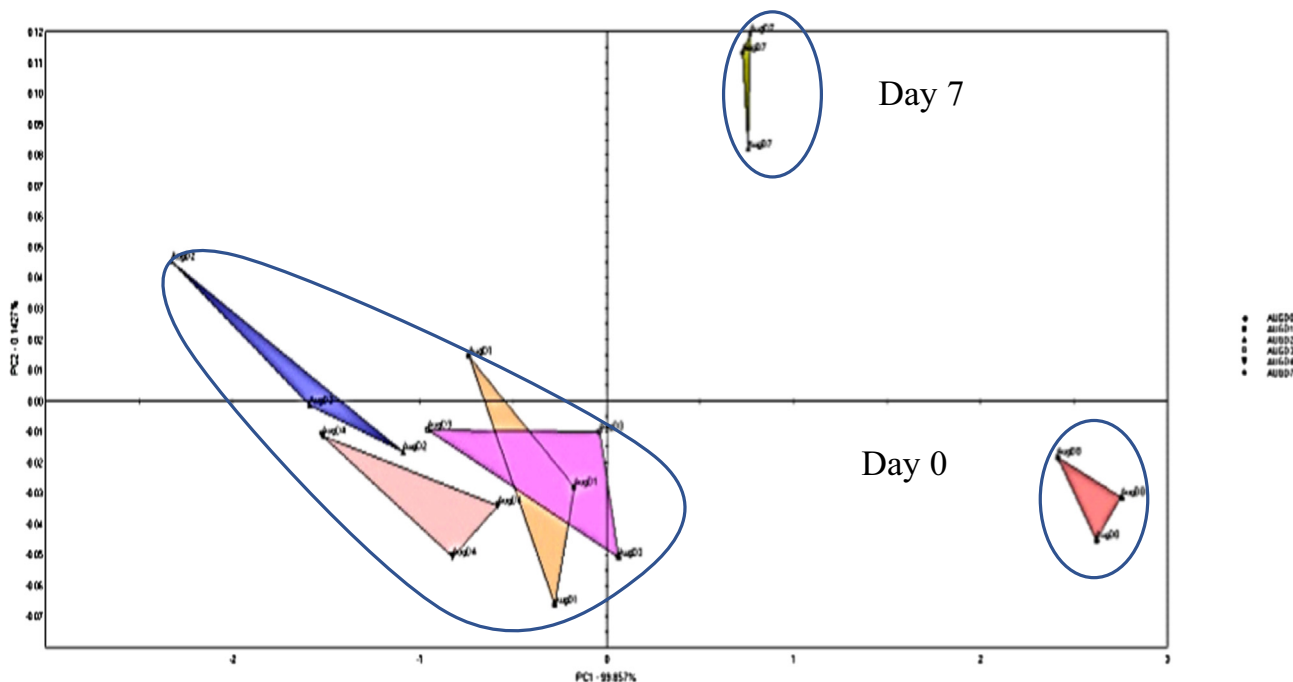


Fig. 3 (continued)

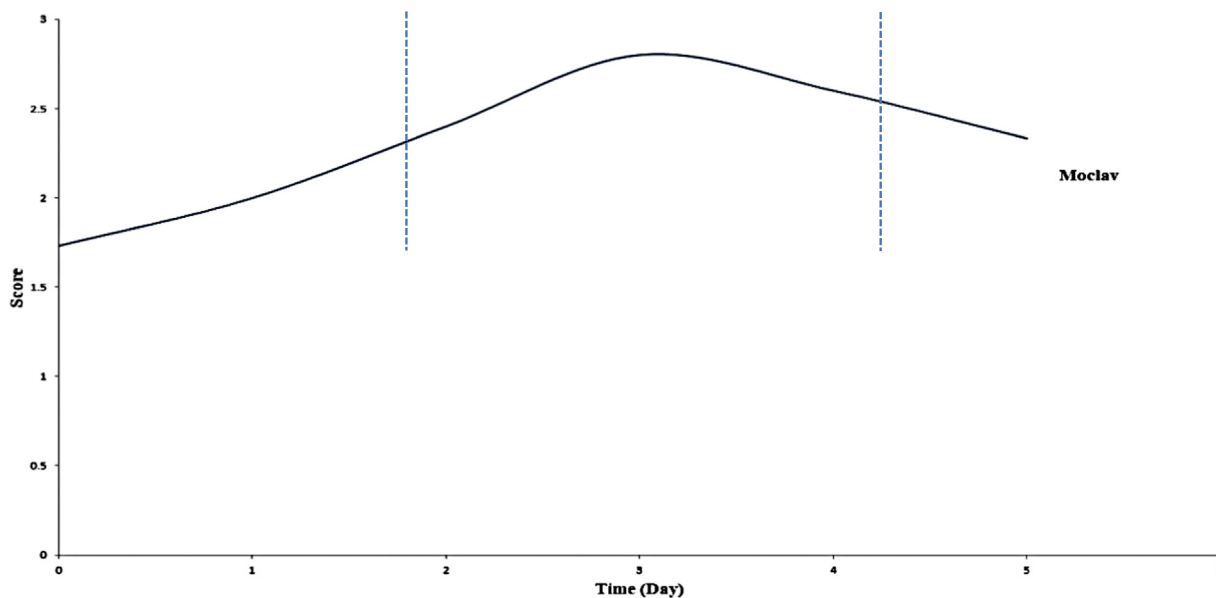


Fig. 4. (A): In-vivo test for Moclav showing the mean response to the 5-point hedonic scale versus time (B): PCA scores plot from the electronic tongue for Moclav.

cine) showed a trend of three areas (flat, exponential growth peak and then a curve down).

Interestingly, ET analysis tool expressed as PCA scores plot showed the same trend for three areas, i.e. the samples of the first day were near each other, then they were far from the first day, and then on the last day they were very close to the first day measurements (Figs. 2–5 (B)). Fig. 6 shows the PCA of all samples measured by ET. The four medicines followed the same pattern.

It can be noted that general trends of suspension taste over time as obtained using either in-vivo or in-vitro (ET) were similar. Both analysis suggested that children did not like the products as dosed

immediately after reconstitution, then they found that the taste better. However, taste deterioration was observed in the fifth day.

4. Discussion

Modifying the taste of oral drugs is one of the most challenges found in the pharmaceutical industry. It can be modified by adding flavouring and sweetening agents or by using a technological agent to improve the bad taste (Mennella and Beauchamp, 2008).

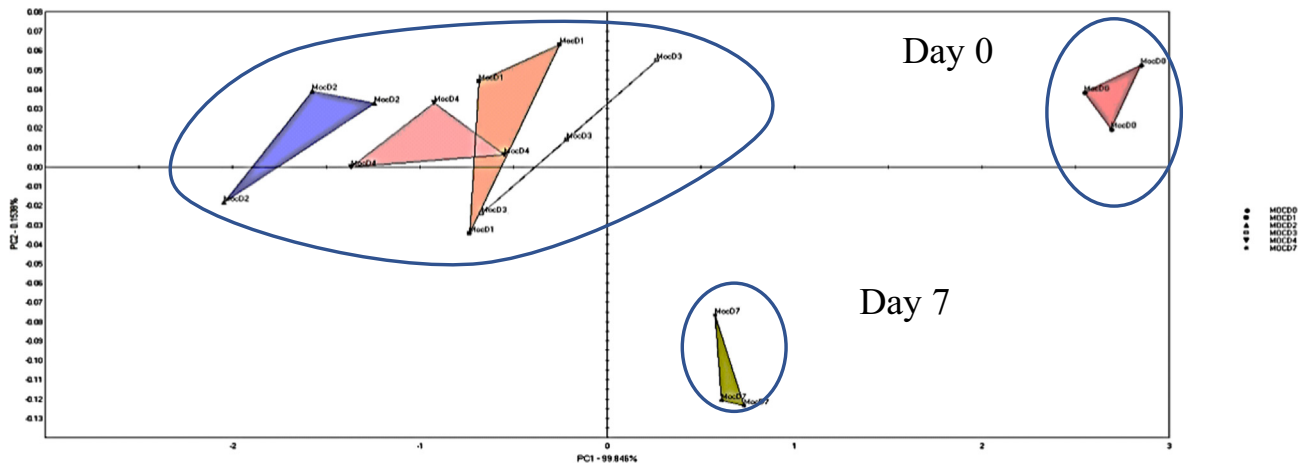


Fig. 4 (continued)

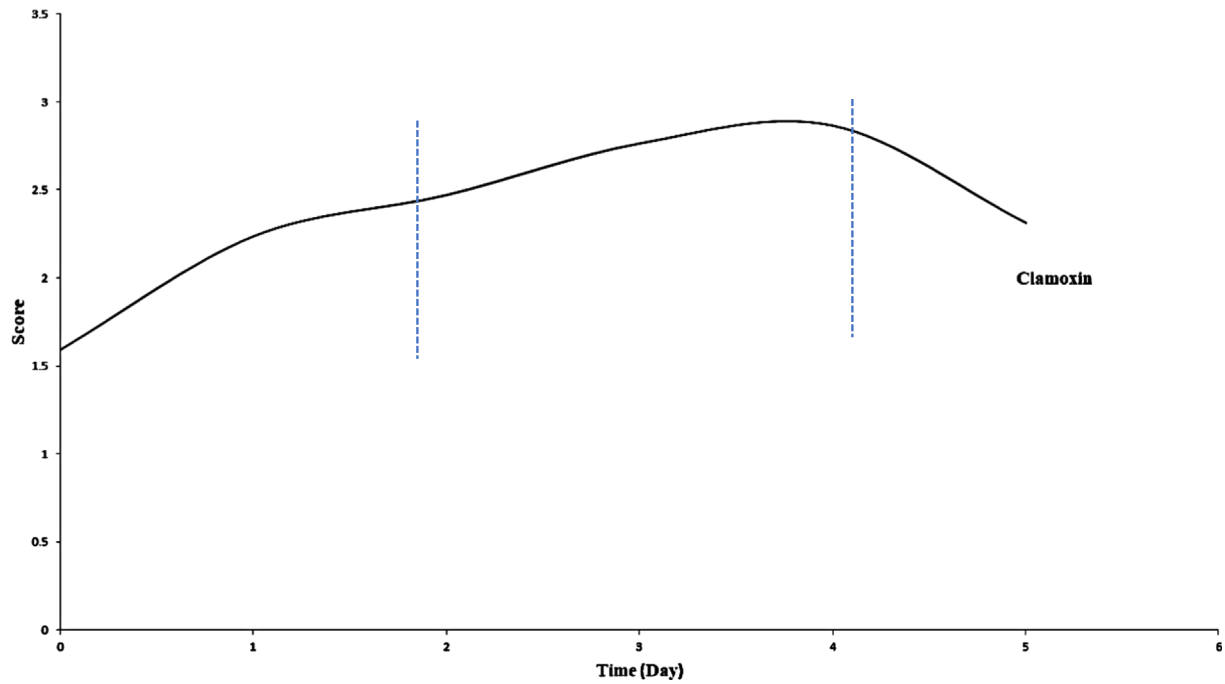


Fig. 5. (A): In-vivo test for Clamoxin showing the mean response to the 5-point hedonic scale versus time (B): PCA scores plot from the electronic tongue for Clamoxin.

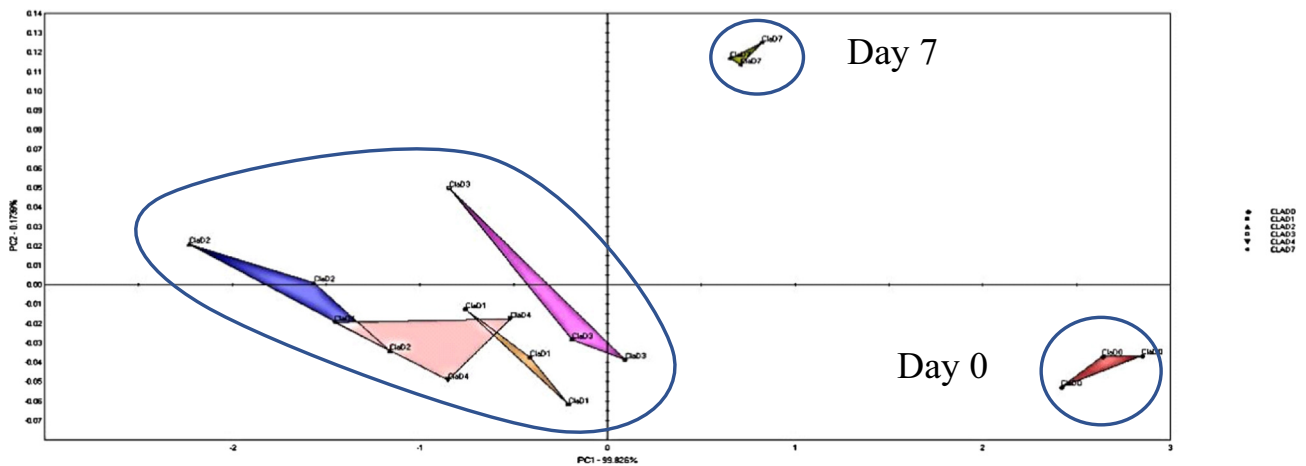


Fig. 5 (continued)

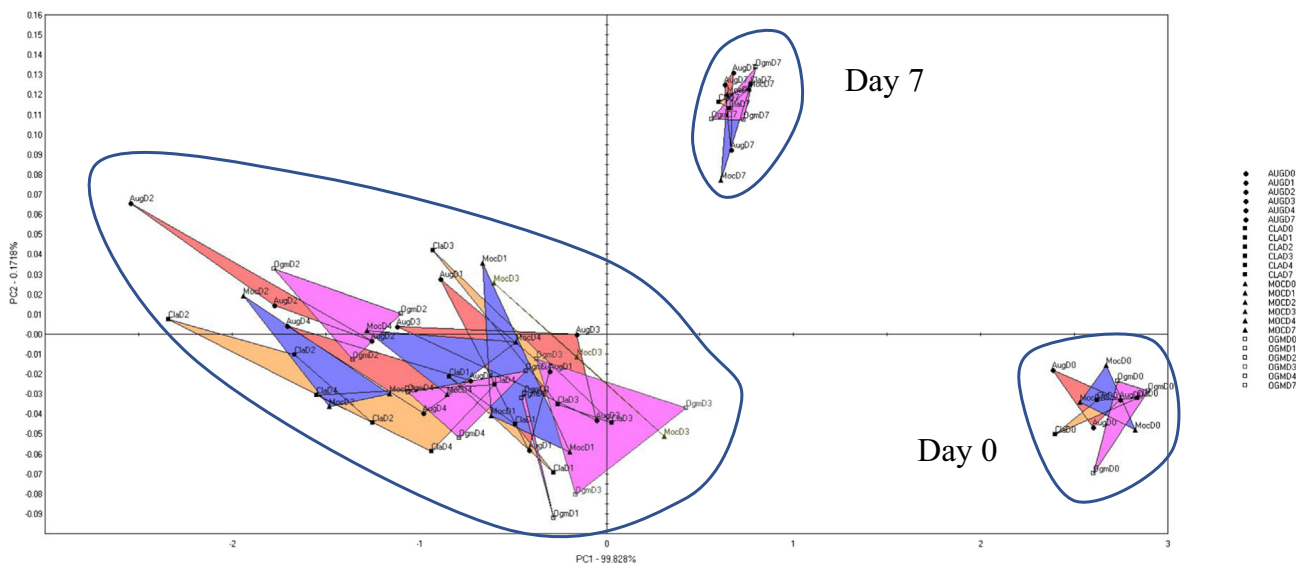


Fig. 6. The PCA of all samples (the four products) measured by the electronic tongue.

While taste evaluation according to a human panel test is possible, unfortunately, it has many limitations, i.e. it depends on patient psychological state, the volunteers are exposed to potential side effects and it requires funding (Committee for Medicinal Products for Human Use (CHMP) 2013). Such drawbacks would be effectively addressed by the emerging tool ET which can be used for testing the taste of many products and evaluating their quality including milk (Winqvist, Bjorklund et al., 2005), oil (Apetrei and Apetrei C 2014), wine (Cet, GonzJlez-Calabuig et al., 2017) and herbal products (Eckert, Lutz et al., 2011). Regarding pharmaceutical products, ET has been tested as a possible method of evaluating taste masking of active ingredients. New sensor types able to evaluate active ingredient taste masking strategies are constantly being developed, one of these was the (Alpha-Astree, Alpha MOS, Toulouse, France) used here (Podrażka, Bącznyńska et al., 2018). In a previous study, the ET was used as a potential tool to identify the quality and the stability of the Cefdinir reconstituted suspensions and it was able to significantly correlate the change in the taste of the suspension to its chemical stability (Abu-Khalaf, Zaid et al., 2019).

As shown from the in vivo panel test results, all suspensions showed the same trend regarding the taste change. A low score of taste was found immediately after the reconstitution (Day 0) which can be explained by the lack of complete dissolution of the sweeteners and flavours as the parents tend to shake the suspension quickly without allowing enough time for complete dissolution. As expected, the taste scores improved in the following three days probably due to complete sugar dissolution. However, a drop of taste scores was observed in days 4 and 5 which may be due to the newly formed degraded ingredients that may worsen the taste of the suspension.

The same trend was shown by in-vitro (ET) test. The distance between the first day and the following days was high. Then at the end of the testing time, the distance between the last days and the first day was less than the other days. This trend suggests that there is a correlation between both in-vivo and in-vitro systems.

So, based on these results, ET can be used as a supplementary tool for decision support in taste evaluation in biotechnology applications.

5. Conclusion

The ET results were similar to those from panel test regarding the changes of the taste during stability period; ET seems to be a promising devise for testing the taste of suspensions after reconstitution.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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