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Impact of sodium lauryl sulfate in oral liquids on e-tongue measurements

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ABSTRACT

During development of oral liquid medicines taste assessment is often required to evaluate taste and taste masking. Electronic tongue analysis can provide taste assessment of medicinal products but should only be conducted with medicines that interact with the instrument without damaging the sensor membranes or interfering with their electrical output so that robust data is generated. To explore the impact of a substance deemed unsuitable for electronic tongue analysis the influence of the anionic surfactant sodium lauryl sulfate (SLS), on the performance of the electronic tongue was conducted using electronic tongues equipped with self-developed PVC based sensors. The results showed a significant impact of SLS on all applied sensor types and an alteration of the sensor's sensitivity. Nevertheless, concentration dependent sensor responses could still be obtained and the sensor performance was not impacted negatively. Assessment of unsuitable substances should therefore be evaluated prior to performing electronic tongue analysis so that their impact is understood fully.

1. Introduction

Taste and taste-masking are critical aspects for the compliance and acceptability of oral dosage forms. An aversive taste of an orally administered medicine might lead to rejection of the medicine intake, especially in pediatric patients (Breitkreutz and Boos, 2007; Davies and Tuleu, 2008). This issue can occur for all orally administered dosage forms either solid or liquid. To reduce the prevalence of refusal and to improve the acceptability taste has become a quality attribute of oral formulations (Sohi et al., 2004). As a quality characteristic the taste has to be assessed in an objective and reproducible way to ensure the reliability and comparability of the obtained results. Besides human taste panels, which are poorly reproducible (Legin et al., 2004), electronic tongue (e-tongue) measurements have been successfully established in evaluating taste-masking of oral dosage forms in early and late phase drug development (Pein et al., 2014b; Woertz et al., 2011b).

E-tongues are electrochemically based instruments equipped with an array of sensors. The sensors are commonly membrane electrodes, which have a polymeric membrane with artificial lipids incorporated (Legin et al., 2004; Toko, 1998; del Valle, 2011; Woertz et al., 2010a). Changes in the membrane potential depend on the formation of an electrical double layer on the charged membrane of the electrodes and define the measurement principle. The lipid/polymer membrane composition is responsible for the varying electric characteristics and varying interaction with the sample solution that the electrodes possess. The electrochemical properties of the membrane, the sample, and the resultant interaction lead to a change in the membrane potential, which in turn is detected as the sensor response in mV and is recorded against a reference electrode (Kobayashi et al., 2010). Commercially available electronic taste sensing systems are distributed by AlphaMOS (αAstree Toulouse, France) and Insent Inc. (SB402 and TS-5000Z, Atsugi-Shi, Japan). Ever since both systems have been qualified according to the ICH guideline Q2(R1) (Pein et al., 2013; Woertz et al., 2010a), they are recognized as valuable tools in pharmaceutical industry for the development of taste-masked drug formulations (Thompson et al., 2013).

Taste-masked oral liquid formulations are complex systems involving numerous functional classes of excipients, e.g. polymers,

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Table 1
Labeling and membrane composition of the applied sensor sets; M = membrane type, S = sensor set, other abbreviations see Section 2.1.2.

Laboratory	Control Sensor Set	'Test' Sensor Set	Plasticizer	Ionophore	Artificial Lipid	Oleic Acid
HHUD	M1S1	M1S2	IPM	CDO	TC, BP	x
	M2S1	M2S2	IPM	HPßCD	TC	
	M3S1	M3S2	IPM	CDO	TC, BP	x
	M4S1	M4S2	NPOE	HPßCD	TC	x
Novartis	M1S3	M1S4	IPM	CDO	TC, BP	x
	M2S3	M2S4	IPM	HPßCD	TC	
	M3S3	M3S4	IPM	CDO	TC, BP	x
	M4S3	M4S4	NPOE	HPßCD	TC	x

sweeteners, flavoring and coloring agents, preservatives, lipids, cosolvents and surfactants (Woertz et al., 2010b). Some of these excipients, such as cosolvents and surfactants, have the potential to interact unfavorably with the polymeric membrane of the sensors and are therefore deemed unsuitable for e-tongue analysis. They may influence the sensor signals, rendering the data unreliable, and could cause irreversible damage of the sensors. This potential risk and limitation reduces the applicability of the e-tongue in performing taste assessment of certain oral liquid formulations. Woertz et al. emphasized the applicability of e-tongue during development of taste masked oral liquids (Woertz et al., 2010b), however, the critical impact of different excipients was not discussed.

At present there is little knowledge on what excipients interact unfavorably with the polymeric membrane and deteriorate the sensors resulting in a sensor response outside of the expected change in membrane potential. Anecdotal information highlights concern for lipids, cosolvents and surfactants but there is no conclusive evidence or specification on concentrations that can or cannot be assessed. The exact knowledge on the effect on the sensor output to various formulations/APIs, which contain these potentially harmful excipients is therefore also limited.

In the present study the influence of the anionic surfactant sodium lauryl sulfate (SLS) on the sensor response to a model oral liquid formulation containing flavoring agent, preservative, and buffer was examined. SLS was selected because it is a commonly used wetting agent and has been utilised in oral products, such as Ceclor® and Exjade® that are administered as liquid preparations at point of administration (Strickley et al., 2008). To ensure that resulting effects are solely due to the impact of one or the other sample component, and not due to the use of different sensor batches, self-developed PVC based e-tongue sensors were applied across two laboratories. These sensors were developed based on a similar composition of the commercial available ones from Insent Inc., since this particular model of e-tongue (SB402, TS5000-Z) is used commonly in pharmaceutical development.

2. Materials and methods

2.1. Materials

2.1.1. Sample preparation

Samples with quinine hydrochloride dihydrate (**QH**, Buchler GmbH, Braunschweig, Germany), cherry dry powder (Symrise, Germany), SLS (KLK Tensachem S.A, Belgium) and methylparaben (Fluka Analytical, Buchs, Switzerland) were prepared using citric acid monohydrate (Sigma-Aldrich, St. Louis, MO, USA) and sodium citrate tribasic dihydrate (Fluka Analytical, Buchs, Switzerland) as buffer medium. Potassium chloride (Grussing, Filsum, Germany), tartaric acid (AppliChem, Darmstadt, Germany), potassium hydroxide (Gruessing, Filsum, Germany), hydrochloric acid (Merck, Germany) and absolute ethanol (VWR international, Darmstadt, Germany) were used for the preparation of the washing and standard solutions for the e-tongue.

2.1.2. Sensor preparation

Polyvinyl chloride (**PVC**, Sigma-Aldrich, Steinheim, Gemany), isopropylmyristate (**IPM**, Cognis GmbH, Duesseldorf, Germany), 2-nitro-phenyl octyl ether (**NPOE**, Fluka Analytical, Steinheim, Germany), trioctylmethyl ammonium chloride (**TC**, Alfa Aesar, Karlsruhe, Germany), bis(2-ethylhexyl) phosphate (**BP**, Sigma-Aldrich, Steinheim, Germany), oleic acid (**OA**, Fluka Analytical, Steinheim, Germany), hydroxypropyl-ß-cyclodextrin (**HPßCD**, Roquette, Lestrem, France), a cyclodextrin oligomer (**CDO**, HHU, Duesseldorf, Germany), tetrahydrofuran (**THF**, VWR international, Darmstadt, Germany), absolute ethanol (Sigma-Aldrich, Steinheim, Germany) and acetone (VWR international, Darmstadt, Germany) were used for the preparation of the membranes for e-tongue sensors (Table 1).

2.2. Methods

2.2.1. Sensor preparation

Different amounts and types of plasticizer, ionophores and artificial lipids were mixed with PVC and the organic solvents to prepare the polymeric suspension for the sensor membranes. The membranes were produced by solvent casting of the polymer mixtures to a Hostaphan® foil (Wiesbaden, Germany) with a coating knife of 1000 µm gap width on a coatmaster (Erichsen, Sweden). Dried polymer membranes were cut into pieces of 1.2 × 0.8 cm and attached to a sensor head blank (Insent, Japan). The sensor was filled with an internal solution of 3.33 M potassium chloride in saturated silver chloride. A silver/silver chloride wire was put into the sensor head functioning as the working electrode (Fig. 1). The prepared sensors were conditioned in standard solution (0.3 mM tartaric acid and 30 mM potassium chloride in distilled water) for 24 h before the measurements.

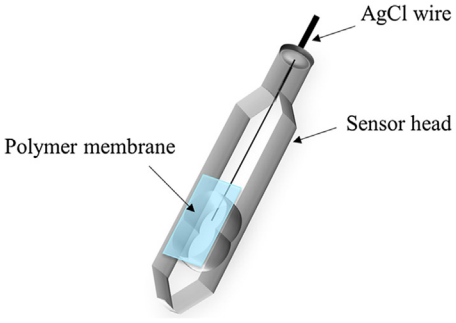

Fig. 1. Electronic tongue sensor equipped with an artificial lipid-based polymer membrane and a silver/silver chloride wire, filled with internal solution.