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Review

Taste-masking assessment of solid oral dosage forms–A critical review

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ABSTRACT

Approaches to improve the taste of oral dosage forms that contain unpleasant tasting drugs are versatile. Likewise, the analytical in vitro and in vivo methods to assess taste-masking efficacy are diverse. Taste-masking has gained in importance since the EU legislation on medicines for children came into force in 2007, and taste-masking attributes are often required by regulatory authorities. However, standardized guidance for the analytical evaluation is still poor. Published protocols rarely consider real conditions, such as the volume of saliva or the residence time of solid oral dosage forms in the mouth. Methodological limitations and problems regarding time point of evaluation, sampling or sample pretreatment are hardly ever addressed. This critical review aims to evaluate and discuss published strategies in this context.

Contents

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1. Introduction

For drug therapy adherence and patient convenience, taste-masking of unpleasant tasting active pharmaceutical ingredients (APIs) is desirable. Many research and developing groups spend tremendous effort on developing taste-masked formulations, whereof several approaches have been derived (Momin, 2012). One taste-masking approach is to construct physical barriers as realized in coated tablets or granules. As tablets are intended to remain shortly in the oral cavity, a coating layer can shield the unpleasant taste of the API from the taste buds in the oral cavity until the tablet has been completely swallowed (Malik et al., 2011; Nakano et al., 2013). Other common approaches are based on the addition of sweeteners, ion exchange resins (Fu Lu et al., 1991) or cyclodextrins (Mady et al., 2010; Preis et al., 2012; Suthar and Patel, 2011). As a substance needs to be dissolved for perception by the receptors located in taste buds on the human tongue, a lower solubility is tantamount to a less bad taste. Therefore, pH modifiers converting a substance into its less soluble or even insoluble form are also used to achieve taste-masking effects (Ogata et al., 2012). With regard to the chemical stability of drug substances, consideration of the effects of mixing corresponding drug formulations with food or beverages is important. For example, some antibiotics are sensitive to a decreased pH (e.g. azithromycin) like present in apple sauce, or to multivalent cations (e.g. tetracycline) present in milk products. Nevertheless, this approach enables a simplified administration to children and elderly patients (Sadrieh et al., 2005), because these groups often face problems in swallowing solid dosage forms. Moreover, increased viscosity of a drug formulation might help to achieve a taste-masking effect by inhibiting drug diffusion to the taste receptors.

Masking unpleasant tasting APIs is doubtlessly desirable, if they are incorporated in solid oral dosage forms, which potentially release the API within the oral cavity. This is even intended for orodispersible solid dosage forms (European Pharmacopoeia, 2008; Food and Drug Administration, 2008). Standardized testing protocols and specification limits are provided by the pharmacopoeia such as adequate disintegration times (Ph. Eur.: 3 min European Pharmacopoeia, 2008, FDA: 30 s (Food and Drug Administration, 2008)), but criteria for disintegration are not useful to judge about the taste-masking efficacy. Drug release specifications might be feasibly adapted for the assessment of taste-masking effects. But while, for example, immediate release dosage forms require a drug release of 80% within the first 45 min, such specifications are not provided for the drug release of orodispersible solid dosage forms. Based on some taste-masking approaches, a delayed release behavior arises within the first minutes of dissolution testing (Cerea et al., 2004). According to a former FIP/AAPS guideline, a drug release of $\leq$10% within the first 5 min of dissolution indicates a successful taste-masking (Siewert et al., 2003). However, this arbitrary threshold is highly dependent on the human perception threshold of each individual drug substance and dissolution methods as such are not applicable to judge about taste-masking effects based on the addition of sweeteners or flavors.

So far, human taste panels are often used for the assessment of taste-masking properties, e.g. in Refs. (Bhoyar et al., 2011b; Cilurzo et al., 2011; Douroumis et al., 2011; Fukui-Soubou et al., 2011; Kasliwal and Negi, 2011; Liew et al., 2012; Mady et al., 2010; Makwana et al., 2010; Malik et al., 2011; Shah and Mashru, 2008a; Sharma et al., 2012; Sharma and Chopra, 2012). But due to ethical and toxicological concerns, conducting human taste panels is questionable, if the drugs of interest are still in the early stage of development. On the contrary, analytical methods offer safe and objective results. Thus, spectroscopic drug dissolution analysis and electronic tongue measurements are often applied to assess the efficiency of taste-masking effects. Using UV spectroscopy, either the dissolution profile of a sample is evaluated or the amount of released drug after a predefined dissolution time is determined. In investigations with electronic taste sensing systems (e-tongues), taste-masking effects are treated by univariate and/or multivariate methods (Guhmann et al., 2012; Hoang Thi et al., 2012; Tokuyama et al., 2009; Woertz et al., 2011b; Zheng and Keeney, 2006).

In contrast to the well-established pharmaceutical techniques to obtain taste-masked formulations, taste assessment lacks precise description. This imbalance is due to the lacking definition of taste-masking and missing standard evaluation tests and specifications. Although some reviews have dealt with the assessment of taste-masking effects in recent years (Anand et al., 2007; Datrange et al., 2012; Sagar et al., 2012; Shet and Vaidya, 2013), the critical aspects coming along with the according evaluation of solid oral dosage forms are rarely discussed (Gittings et al., 2014; Woertz et al., 2011a).

As the application of analytical methods for taste-masking assessment gained importance, since the EU legislation on medicines for children came into force in 2007 (Breitkreutz, 2008; European Union, 2006), this review assembles and critically discusses recent approaches of assessing taste-masking properties of solid oral dosage forms (granules, microspheres, pellets, tables and film formulations). Manuscripts have been considered, if the assessment was performed with human taste panels (defined as in vivo evaluation) and/or UV spectroscopy and/or electronic tongue measurements (defined as in vitro measurements). UV spectroscopy measurements comprise in this context on-line and in-line UV-monitoring of the drug dissolution as well as off-line UV detection or high performance liquid chromatography (HPLC) measurements after sampling. Electronic tongue measurements have only been considered, if they were carried out with at least one of the commercially available instruments (Insent or αAstree).

2. In vivo evaluation of taste-masking

Although there are standardized protocols for taste evaluation (DIN10959, 1998; DIN10961, 1996; DIN10969, 2001; ISO3972, 1991), so far no standardized protocol exists for the evaluation of taste-masking. Rather, the protocols described in literature differ in their procedures, particularly with regard to the panelists, the administration of the drug formulation and the time point(s) to assess the taste-masking effects (Table 1).

2.1. Panelists

As summarized in Table 1, investigated studies have been conducted with 4–30 healthy adult human volunteers. If the ages of the gender-mixed panelists were reported, they varied between 18 and