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Research paper

Taste evaluation of a novel midazolam tablet for pediatric patients: In vitro drug dissolution, in vivo animal taste aversion and clinical taste perception profiles

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ABSTRACT

Harmonized methodologies are urgently required for the taste evaluation of novel pediatric medicines. This study utilized *in vitro*, *in vivo* and clinical data to evaluate the palatability of a novel midazolam chocolate tablet. *In vitro* dissolution experiments showed the crushed tablet to release within 5 min 1.68 mg of midazolam into simulated saliva. This translated to a drug level of 0.84 mg/ml in the oral cavity, which would be higher than the midazolam bitterness detection threshold concentration of 0.03 mg/ml determined in a rat 'brief access taste aversion' (BATA) model. The visual analogue scale scores of patients aged 4–16 years prescribed with midazolam pre-surgery showed a clear preference for the midazolam chocolate tablets (3.35 ± 1.04, $n = 20$) compared to the control midazolam solution (1.47 ± 0.62, $n = 17$). The clinical data was in agreement with the *in vivo* rodent data in showing the novel chocolate tablet matrix to be effective at taste-masking the bitter midazolam.

1. Introduction

In pediatric patients, the unpleasant taste of a medicine is one of the commonest causes of treatment barrier American Academy of Pediatrics, Division of Health Policy Research, 2017, and the importance of building palatability into pediatric medicines is now recognized by the pharmaceutical industry Zajicek et al., 2013 and the regulatory authorities Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on products for paediatric use and amending Regulation (EEC) No 1768/92, 2006; European Medicines Agency, 2006. However, there is no specific regulatory framework for palatability assessment, which has resulted in a lack of harmonization of taste evaluation methodologies applied in the development of pediatric medicines Thompson et al., 2013; Davies and Tuleu, 2008.

The simplest taste evaluation methods for peroral pediatric medicines is to determine the *in vitro* drug release profile of the medicines in simulated physiological fluids, the rationale being that only the freely soluble drug molecules can interact with taste receptors. While cheap and readily accessible, this method is better suited to solid medicines, not solution formulations, and provides a measure of taste only when human perception of the tastant is known to some extent (e.g. as a taste threshold concentration). Currently, there are no regulatory-defined parameters to simulate drug release in the oral cavity from medicines. Published studies that have utilized the *in vitro* drug dissolution method to evaluate medicine palatability have employed a range of dissolution medium (water Ishizaka et al., 2008 to pH 6.8 phosphate buffer Shahzad et al., 2011; Shishu and VR, 2009), receptor fluid volume (10 ml Yan et al., 2010 to 900 ml (8)), and dissolution time (2 min (8, 9)–5 min Ishizaka et al., 2008).

Electronic taste evaluation may be a better alternative Mohamed-Ahmed et al., 2016 as it can profile the taste characteristic of the drug molecule via an array of sensors Woertz et al., 2011a. Compared to *in vivo* models, electronic sensors also provide a more objective and

Abbreviation: BATA, brief access taste aversion

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consistent taste evaluation without incurring the ethical and safety concerns associated with using animal and human participants. Electronic tongues are, however, limited by their application to assess only aqueous solutions, and the sensor sensitivity can be affected by formulation pH and excipients Woertz et al., 2011b.

An *in vivo* model that exploits the natural defense mechanism in most animals to avert bitter-tasting substances has also been developed for the palatability testing of medicines Bhat et al., 2005. Mildly water-deprived rats are presented with the liquid tastant, and an IC_{50} dose, defined as the tastant concentration that causes a 50% drop in licking frequency compared to water, is determined. This model is advocated for novel lead compounds whose toxicology has not been adequately elucidated to safeguard taste evaluation in humans. Products for evaluation by this method have to be liquid formulations of appropriate viscosity, and if they are suspensions, to have particles below a threshold diameter to enable the liquid formulations to flow freely through the sipping tube for the animals to lick. It is difficult to establish the accuracy of taste evaluation in animal models because the *in situ* drug concentration in the oral cavity cannot be measured accurately. Even if this concentration is measurable, it may still not correlate with 'palatability' and 'acceptable taste' as these perceptions are dependent also on other factors, e.g. the age and taste receptor expression of the animal model used.

The most direct measurement of palatability of a product is to conduct taste evaluation in humans, ideally in the specified pediatric age groups to account for age–related sensitivities towards bitter and sweet tastes Mennella et al., 2005; Mennella et al., 2014. Pediatric taste studies are, however, associated with significant methodological and ethical barriers around participant recruitment. Parents and clinicians may resist a taste trial where a healthy child may accidently ingest a pharmacologically active agent, especially a novel yet-to-be-approved potent agent. On the other hand, parents and clinicians struggling to achieve treatment compliance in a child who requires the intervention of an unpalatable drug may be more inclined to support a clinical trial to evaluate a potentially better tasting product of the drug. In such cases, however, the application of a cross-over study design with placebo or comparator tastant could be unethical. Children may also be less able than adults to describe taste, and taste trials involving children may have to rely on scales of assessment that are yet to be validated for taste evaluation, e.g. the 5-point facial hedonic scale and visual analogue scales Davies and Tuleu, 2008.

Midazolam is a bitter drug that has caused considerable grief in pediatric hospitals. It is widely prescribed as a pre-medication aimed at calming young patients scheduled for surgery and dental procedures. Taste masking of midazolam has been challenging, with both the commercial and extemporaneously compounded oral midazolam syrups known anecdotally for high rejection rates due to poor taste. Rejection of the medicine presents particular difficulties in children who are very anxious or uncooperative in the preoperative setting, e.g. autistic children. In the event of treatment failure, the uncooperative children may have to be physically restrained for the induction of anesthesia, posing, particularly in older children, significant safety risks for the patients, accompanying parent/guardian and attending medical staff.

Our laboratory has developed a novel chewable chocolate-based tablet containing 5 mg of midazolam HCl for use in children. These are small tablets measuring 10 × 5 × 5 mm with 3 score lines to facilitate dose division (Fig. 1A). The aim of this study was to provide a first-in-kind comprehensive evaluation of the palatability of a pediatric dosage form using a range of methodologies and the midazolam chocolate tablet as a model formulation. We applied the *in vitro* dissolution test, the rat brief-access taste aversion (BATA) model and a clinical trial involving patients aged 4–16 years of age to the taste evaluation of the chewable midazolam chocolate tablet. The electronic tongue was excluded because it would involve conducting a dissolution experiment for the midazolam chocolate tablets and analyzing filtered aliquots of the dissolution medium in the E-tongue. The filtered aliquots would not provide an accurate measure of the effectiveness of the chocolate matrix in masking the taste of the released drug. In this regard, the E-tongue would not offer significant advantages to the dissolution experiments in evaluating the taste of the formulation. A correlation of the *in vitro* dissolution profile, animal taste aversion profile and pediatric taste scores for the chewable tablet, together with issues associated with each of the methodologies, is discussed in the present study.

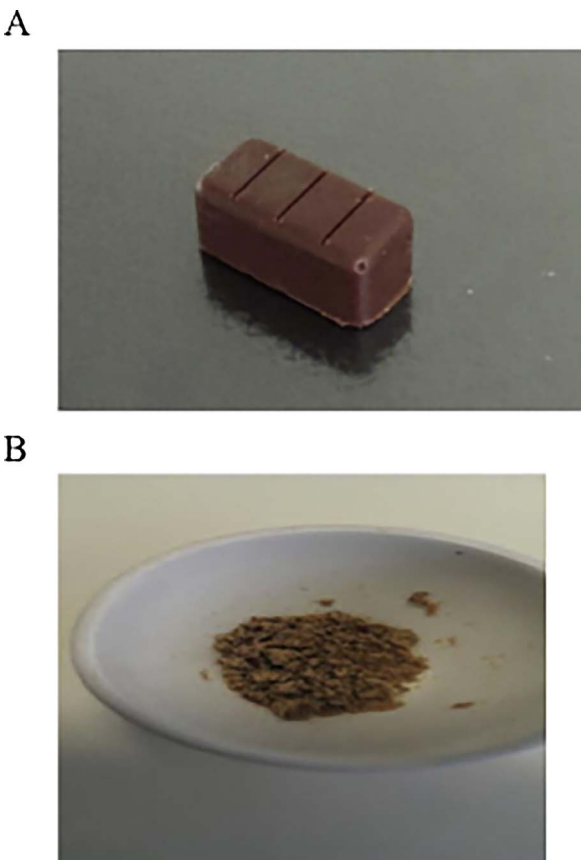

Fig. 1. The midazolam chocolate tablet (A) Intact tablet; (B) Crushed tablet for *in vitro* dissolution studies.

2. Materials and methods

Midazolam hydrochloride (HCl) (BP grade, Cambrex Profarmaco Milano, Italy) was used as received. All other chemicals were of analytical grade. Deionized water (PSI Water Filters, Launceston, TAS, Australia) was used throughout.

2.1. Preparation and storage stability of chocolate-based chewable tablets

Chewable tablets each containing 5 mg of midazolam hydrochloride and measuring 10 x 5 x 5 mm were prepared by a melt moulding technique using generally regarded as safe excipients that included dark chocolate (Nestle Australia Ltd, Rhodes, NSW, Australia), hydrogenated castor oil, xanthum gum, polyethylene glycol 1450, and steviol glycosides. All ingredients, except for the dark chocolate, were of pharmaceutical grades (BP or USP) and obtained from registered pharmaceutical suppliers in Australia.

2.2. In vitro drug dissolution profiles

In vitro drug dissolution was conducted in triplicates using a paddle rotating speed of 50 rpm (Varian VK 7010 Dissolution Apparatus, Agilent Technologies, Mulgrave, Victoria, Australia). Tablets weighed