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A review of *in vitro* and *in vivo* methods and their correlations to assess mouthfeel of solid oral dosage forms.

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A teaser: This review analyses the relationship between instrumental and human data used to assess the mouthfeel of solid oral dosage forms to provide recommendations on the most appropriate methods to use in future studies.

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Abstract

The oral sensory perception of medicines is an important quality attribute that can influence adherence to medication. A systematic review identified studies reporting both *in vitro* and *in vivo* data on the mouthfeel of solid oral dosage forms. Fifty-six studies were identified and included in the analysis. Orodispersible tablets were the most commonly studied formulation (32/56 studies). *In vivo* studies were typically conducted using untrained healthy adult volunteers where sample sizes ranged from 3-75 participants. Only 8 studies reported a numeric correlation between the *in vitro* and *in vivo* data presented. This review highlights opportunities for the development of a standardised approach to assessment of mouthfeel to enable the development of optimised oral pharmaceutical products.

Introduction

All sensory attributes (including mouthfeel, taste, smell and appearance) affect palatability and a patient's willingness to take their medicine [1,2]. Palatability has been reported to affect the acceptance of medicines where taste was reported to be the most significant attribute and has been the subject of several reviews [3-9]. However, the mouthfeel, specifically texture of medicines has previously been identified as a barrier in the oral acceptability of medicines yet there has been limited work on this topic [10,11]. In sensory science, mouthfeel is defined as a physical sensation which is created in the mouth by a product, as distinct from taste [12]. It encompasses sensations of touch, pain and temperature (in comparison, texture is limited to the attributes of a product perceptible by touch). As mouthfeel involves all aspects of oral interactions with a dosage form, the overall perception is often complex and not limited to a single sensation. Assessment of the acceptability of medicines is a relatively new regulatory concept, where regulatory guidance introduced for paediatric medicines mandates acceptability testing for new products designed for children [1]. Despite the surge of interest in acceptability/palatability assessment, there is limited guidance on appropriate and reliable testing strategies.

Key mouthfeel attributes associated with the ingestion of medicine include lubrication; hardness; adhesiveness; cohesiveness; grittiness and disintegration. Mouthfeel perception is affected by the presence of saliva and intensity of mastication/chewing of the product which leads to disintegration and dissolution of solid oral dosage forms and thus to changes in the sensory perception of the product over time. Textural changes relate to the attrition of the dosage unit and the sensation of particulate matter as well as release of viscous or adhesive materials from the formulation. These multifactorial parameters make the development of *in vitro* and *in vivo* testing methods complex.

Mouthfeel attributes of oral medicines can be evaluated using sensory (*in vivo*) or instrumental (*in vitro*) methods. It is recognised that human sensory analysis is the "gold-standard" to assess the sensory perception of medicines, however, there is limited experience in the conduct of such studies within pharmaceutical product development. Sensory studies are commonplace in food sciences research, where a trained human panel evaluate sensory attributes of materials using reference products as a control. Panellists are extensively trained in sensory assessment and use a clearly defined lexicon of the terminology to assess each sensory attribute [13]. Sensory assessment differs from consumer testing; consumer testing measures a hedonic response to a product thus a holistic evaluation of the product rather than evaluation of specific defined attributes. For example, a sensory panel will provide quantitative data on the sweetness of a product whereas a consumer panel will report their degree of liking of the product under test. In the food sciences, consumer responses can be correlated to sensory attributes via the sensory panel to inform product development.

The assessment of sensory attributes of medicines largely differs compared to food, as medicines are typically retained in the mouth for a much shorter time and the expectation from medicine is very different to that experienced with food. A key factor in the design of a sensory study is the definition of the attribute under evaluation and setting a specification target for this attribute (e.g. hardness) [14], which is challenging for oral medicines due to the infancy of this field of research and practice.

The only pharmacopoeial test that relates to a sensory attribute is the disintegration test that has been adapted from the disintegration test for an immediate release conventional tablet to evaluate orodispersible products where the conditions are far from those found in the oral cavity. The typical volume in pharmacopoeial apparatus is > 800 mL compared to 0.7 mL of saliva in the oral cavity [15].

There is also an impact when using water compared to more biorelevant fluids (e.g. artificial saliva) as this can affect the solubility and disintegration of materials [16]. This divergence in methodology to assess oral disintegration is well recognised with a recent paper comparing several reported methods to identify the one that gave the best correlation to *in vivo* data for a set of 6 tablets [17].

In vivo acceptance/palatability studies are associated with long timelines; high costs; the willingness to navigate complex ethical processes; and high inter-subject variability, therefore there is a need to better understand how *in vitro* methods can predict *in vivo* textural mouthfeel attributes of medicines. It is recognised that *in vitro* methodologies possessing high prediction power for sensory attributes would reduce the time and cost of drug development. Many *in vitro* methods to assess mouthfeel have been reported in the literature, yet often the choice has stemmed from the availability of apparatus and expertise within an organisation with no continuity in methodology or agreement on a standardised technique. As sensory analysis is a relatively new aspect of pharmaceutical product design and development, it is important to understand the relationship between instrumental and human data, and then apply this knowledge to improve the development of more acceptable/palatable medicines.

The aim of this review is to highlight the range of both *in vitro* and *in vivo* methodologies used to assess mouthfeel attributes of solid oral dosage forms. A detailed analysis of methodologies used for specific sensory attributes will guide the choice and development of suitable *in vitro* and *in vivo* methods to ensure acceptable textural attributes of solid oral dosage forms under development.

Identification of relevant literature

Search strategy

A systematic and comprehensive literature search was conducted covering the time period from January 1990 to April 2020. The following databases were searched: Web of Science, SCOPUS, PROQUEST and EMBASE. The terms used to search the databases included: (‘mouthfeel’ OR ‘texture’ OR ‘acceptability’ OR ‘palatability’ OR ‘oral perception’) AND (‘medicine’ OR ‘drug’ OR ‘oral dosage form’ OR ‘granule’ OR ‘tablet’ OR ‘odt’ OR ‘odf’ OR ’orally disintegrating tablet’ OR ‘orally dispersible tablet’ OR ‘orally dispersible film’) AND (‘rheology’ OR ‘tribology’, ‘texture analysis’ OR ‘disintegrate’ OR ‘mechanical property’) AND (‘oral’ OR ‘mouth’ OR ‘buccal’ OR ‘tongue’) as well as the derivatives of these terms.

Inclusion and exclusion criteria

Only journal articles including *in vitro* and *in vivo* results on textural properties of solid oral dosage forms were eligible for inclusion in the review. Papers that studied only taste or used animal models (for *in vivo* aspects) in their experiments were excluded from the review. Only papers that included original research where *in vivo* data was part of the study were included in the subsequent analysis.

The searches were performed by JH and AA and the decision on inclusion was made by all three authors.

Data Extraction

The study characteristics, population demographics and outcomes of interest were manually extracted from each study by a single reviewer, a subset was checked by HKB to ensure data capture was accurate. Where possible statistical analysis was undertaken on the resulting data yet there was

a great deal of variability in the reporting thus qualitative descriptions of outcomes of interest are also presented within the results.

Analysis of literature identified

In total 56 studies were identified where instrumental and human sensory data of mouthfeel were available on solid oral medicines. Figure 1 shows the flow of our search and the results before and after applying the inclusion-exclusion criteria.

Formulations investigated

Table 1 lists the mouthfeel attributes according to the formulations used as test samples within the studies identified from the literature search. Formulations most often reported were those with prolonged residence in the mouth, as compared with conventional tablets. Longer residence in the mouth, inevitably, results in more pronounced sensory perception, hence the increased research interest where disintegration time was the most reported attribute. The nomenclature in the literature is not unified for orodispersible, orally disintegrating or orally dispersible tablets with these terms being used interchangeably, all are also abbreviated to ODT. Following European Pharmacopeia 10.0 they will be referred to as orodispersible (ODT) hereafter [18]. ODTs were the most commonly studied formulation investigated in more than half (32/56, 57.1%) of the studies.

In vivo methodologies reported

In vivo cohort demographics

The demographics of the human participants involved in the *in vivo* assessments of mouthfeel are provided in **Error! Reference source not found.**. The majority of studies were conducted in healthy volunteers, only one study involved volunteers with a history of swallowing difficulties, and 9/56 studies did not report the status of the participants' health. The age of participants was reported in 24/56 studies where the ages ranged from 18 to 80 years; 9 papers only reported the average age and 22 papers did not state the age of the participants. The gender of the participants was reported in 35/56 studies. There were 11 studies using a single gender (7 male only and 4 female only); in 16 studies there were more female participants compared to male; 4 studies with more male participants and 4 studies that were balanced. The sample size used for the studies ranged from 3-75 participants with a mean value of 16.5 and a median of 12.

In vivo tools used

A variety of tools were provided for participants to assess their sensory perception of palatability and mouthfeel of tested samples. A brief overview of the tools used is provided in Supplementary **Error! Reference source not found.**. By far, the most commonly reported tool was a scale where participants rated given mouthfeel attributes. In most studies, sensory attributes were rated by participants on structured multiple-point scales (e.g. 5-point scale). The scales which were marked with hedonic terms (e.g. *very bad – very good, disliked – liked*) allowed participants to express their hedonic subjective opinion. While on the scales marked with intensity modifiers (e.g. *low – high, none – strong [roughness])* or antonyms (e.g. *smooth – gritty*) participants could provide an objective description of the sample. Several papers created bespoke scales; where mixed attributes were used

on a single scale, in these cases interpretation can be complex, e.g. 4-point scale with scores: gritty, acceptable, good, excellent [19]. The second most reported type of scale was continuous scale, for example, a visual analogue scale (VAS). Free text description was reported only as a supplementary method of data collection.

In vitro methodologies reported

There are no standardised instrumental techniques that allow objective measurement of texture/mouthfeel of solid oral dosage forms; therefore, multiple varying approaches have been reported. Only 8 papers reported a numeric correlation between in vitro and in vivo data, yet data was available to provide a numeric correlation (R^2calculated as a linear correlation between the *in vitro* and *in vivo* data) in an additional 15 papers. No non-linear relationships were reported to correlate in vitro and in vivo data. In 37 papers evaluation of *in vitro* and *in vivo* disintegration time and their correlation (non-numerical) was reported. Seventeen papers clearly stated relationships between *in vitro* measurements and *in vivo* attributes, other than disintegration. Twenty-seven papers reported using *in vitro* techniques with a potential to correlate with sensory perception but did not further examine the correlation to the *in vivo* data. This section reviews the *in vitro* tools reported in the literature. The details of methodologies used are grouped thematically based on the sensory parameter under test and are presented in the tables below.

Disintegration

Although disintegration time is not a textural parameter in itself it can influence the perception of mouthfeel for orodispersible products. Disintegration time was the most commonly reported endpoint to compare *in vitro* and *in vivo* methods. This is likely to be a result of existing requirements to measure the disintegration time of orodispersible formulations that prompts research in this area (disintegration within < 3 min – [18] Eur. Pharm.10.0., or ; < 30 seconds – FDA [20]). As compendial disintegration methods do not reflect the anatomy and physiology of oral cavity, multiple more biorelevant methodologies have emerged to provide better correlation with *in vivo* data. This divergence in methodology has previously been reviewed [17], [21].

The *in vitro* methodologies found in this literature search that include a correlation of disintegration time with human data are presented in Supplementary Table 3. All formulations assessed were either orodispersible tablets or films. The volume, media and temperature used in *in vitro* methods were not consistent between papers: the volume ranged from ~30 µL to 1000 mL; media used included water, artificial saliva, ethanol:water or phosphate buffer; the most commonly reported temperature was 37°C, but 25°C or room temperature was also reported. Only 8 of the 56 papers reported a correlation coefficient value. Where correlation values were not provided, these have been calculated for this manuscript assuming a linear relationship between variables.

Despite the variability in the methodology used, good correlations were shown in several studies where the apparatus varied (R^2 values close to 1). It is complicated to identify the most promising method from this data as the range of formulations evaluated and test conditions will determine the output. There is also a potential for bias in the design and conduct of studies as only 3 were double-blind studies. A previous review suggested that a biorelevant method designed by Narazaki et al [22] gave the best correlation to human data, and in general biorelevant systems were better than pharmacopoeial methods [17].

There is scope to correlate a range of *in vitro* data including wetting time; water absorption ratio; contact angle and porosity (properties that determine how the formulation interacts with moisture); to the dynamics of dosage form disintegration in the mouth; yet few studies explored the relationships between these parameters.

Grittiness/roughness

In the sensory assessment of oral pharmaceutics, the terms grittiness and roughness are often used interchangeably. The interchangeable use is incorrect as, by definition, roughness relates to a degree of irregularity/unevenness of the product's surface [23], while grittiness refers to the perception of particles/granules and is usually a bulk characteristic [24]. A sensation of both roughness and grittiness can occur when a product is administered as a powder/multiparticulate formulation; disintegrates in the mouth or is chewed; hence, these formulations can be discussed together. Both, disintegration and chewing result in a breakdown of the structure to smaller particles that can then be swallowed either in this state or in a cohered state when mixed with saliva. The rate and resulting size of disintegrated fragments are likely to affect the sensation of grittiness and roughness upon ingestion of this type of dosage form. Indeed, the size of particles/granules was reported to relate to the perceived grittiness and roughness of ODTs [25], multiparticulate formulations [25-27] and chewable tablets [28] (Table 2). As excipients constitute a major fraction of the solid oral dosage form mass, it is obvious that excipient type and ratio affects grittiness/roughness, as reported in several studies [29] [30] [31] [32] [33] [34]. Consequently, the physical characterisation of API, excipients as well as intermediate products (e.g. granules/pellets for tabletting), is a method of choice for prediction of grittiness and/or roughness of the final products. Apart from particle size distribution, several methods, like particle hardness, sphericity and morphology (with optical or scanning electron microscope, SEM), have been reported, although these factors have not been directly linked to these mouthfeel attributes.

Unpleasant grittiness of an solid oral dosage form can be mitigated by co-administration with a liquid/semiliquid vehicle (e.g. [35] and [26]). While thickened fluids were found to minimise the sensation of grittiness of multiparticulate formulations of different sizes, water as a vehicle was not sufficient [26]. No studies on vehicles for co-administration with ODT were found.

Most hard foods are chewed until the particles remaining are less than 2 mm prior to swallowing [55]. A smooth preparation of a tablet dispersed in water prior to administration is the one where the particles pass through a sieve screen with a nominal mesh aperture of 710 µm [56]. While for ODT the size of core granules above 264 µm was reported to result in a rough mouthfeel [25]. This size, however, is far above the sensitivity of the tongue; with particles as small 6-10 µm being perceived [57].

In vitro methods that analyse the shape and sphericity of granules, or surface morphology of the final dosage form can reveal information about roughness and grittiness yet there was little effort to correlate these measures to *in vivo* data.

Adhesiveness/Cohesiveness

Adhesiveness (synonymously termed stickiness) reflects the extent to which a material adheres to the tongue, teeth or palate. It can oppose lubrication as well as impede clearance from the oral cavity. To measure adhesiveness there is a need to manipulate the product to replicate chewing and mixing with saliva; this manipulation can change the properties of the material under test. Adhesiveness is typically measured as the force required to separate the material under test from a

representative oral component (teeth, tongue or palate). Adhesiveness can be both a positive and negative quality, depending on the type of product (e.g. mucoadhesive tablet vs. ODT).

Cohesiveness refers to the adhesion of the material under test to itself; often during the ingestion of food it is chewed and mixed with saliva to form a cohesive bolus that is easier to swallow compared to several smaller items. This can be complex to measure and often the material is measured at several stages to replicate chewing and mixing with saliva using rheology or texture analysis.

In food sciences, adhesiveness and cohesiveness are measured by tensile testing apparatus or texture analysers; similar equipment has been adapted for various solid oral dosage form testing (Table 3). Only one paper reported a significant correlation between *in vitro* and *in vivo* stickiness, which was for an ODF [58].

Hardness/softness

The force required to bite or chew food is of importance for those materials designed to be chewed prior to swallowing. Most solid oral dosage forms are designed to be swallowed without chewing however chewable tablets and chewing gums are obvious exceptions. Hardness/softness of these formulations was related to the composition of the dosage form (**Error! Reference source not found.**) [28,53] . Instrumentally, hardness/softness was measured using compression cycles which imitate a bite (e.g. force required for deformation of a sample) [53].

The sensory attribute of hardness/softness can be linked to other textural properties, in one *in vivo* study participants were asked to rate the consistency and chewability of the gum which is related to the hardness but not a direct measure of this property [53].

Oiliness

Perception of oiliness was mentioned only in one study. It was specific to an emulsion-based formulation, where low stability of the emulsion under mastication resulted in an oily mouthfeel [28]. The oiliness of the soft chewable tablet was related to the type and ratio of the emulsifier used in the formulation [28]; this study is a good example of case-specific optimisation of product mouthfeel.

"Consumer insights" into the palatability/mouthfeel of formulations

As stated in the introduction, sensory analysis provides a quantitative measure of an individual attribute, however, consumer feedback is related to a hedonic experience of the whole product. In the reviewed literature the terms palatability, mouthfeel and acceptance were used interchangeably, as a measure of participants' subjective hedonic and holistic opinion of the formulation under test. The majority of papers failed to include a definition of palatability, mouthfeel or acceptance. In general, these terms were used appropriately, yet there were some examples of incorrect use, e.g. palatability reported as a measure of ease of taking the formulation [42].

Palatability is one of the key acceptability attributes of oral medicine. It is defined as "the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth)" [1]. Hence, palatability is a hedonic evaluation that is subjective in nature.

Several studies attempted to relate palatability/mouthfeel/acceptance to a specific *in vitro* parameter, like granule/particle size [61] [25], coating thickness [62], or proportion of insoluble materials [61] (Table). In these cases, the palatability/ mouthfeel/acceptance was assumed to be driven by a dominant attribute like grittiness/roughness. However, it should be recognized, that for the majority of formulations the palatability is a function of multiple sensory attributes rather than a single factor. Thus, interpretation and correlations between *in vitro* and *in vivo* data are complex and a single *in vitro* test to predict palatability is unlikely to exist.

An exemplary study that included multiple parameters was reported by Casian et al. [36]. In this study, the authors predicted the palatability of ODTs using partial least squares (PLS) modelling, which is a high-throughput predictive statistical method. The model was built using a set of ODTs selected by a design of experiments (DoE) approach. The data input used to train the model was based on formulation characteristics (including filler ratio or granule size), multiple parameters obtained via texture analysis testing, and *in vivo* sensory data. This approach demonstrated a reliable prediction of the holistic palatability of ODTs.

Ease of administration/swallowing

For conventional tablets (which are swallowed whole) the ease of administration is understood as the ability of the patient to swallow the formulation, and it is mainly attributed to the size of the formulation [27]and [1,2]. The regulatory definition of acceptability has been reported as “an overall ability of the patient and caregiver (defined as ‘user’) to use a medicinal product as intended (or authorised)” [68] and “the ability and willingness of a patient to self-administer, and also of any of their lay or professional caregivers, to administer a medicinal product as intended” [2]. Thus, the ability to administer and swallow a solid oral dosage form is fundamental for its acceptance.

A range of factors come into play for a formulation which disintegrates/dissolves/is chewed in the mouth and then swallowed gradually. In such cases, a barrier to administration may arise from the need to use water (with an ODT) or the fragility of the formulation (of an ODF) (Table 5). While ease of administration is relatively easy to evaluate using a human panel, it is difficult to replicate these processes *in vitro*. To date, only two papers reported a relationship between *in vivo* and *in vitro* data for the ease of administration/swallowing [27] [69] (Table 5). A notable example is the throat model which mimics the process of swallowing [69]; the authors reported a relationship between speed of bolus ejection in the model and perception of ease of swallowing of multiparticulate formulation in a viscous vehicle. Although the relationship was not linear, the model correlated to sensory studies and enabled an understanding of the mechanisms involved in swallowing oral medicines.

Time-dependent sensory assessment

The sensory perception of oral medicine can extend beyond administration, the sensation in the mouth can linger and be unpleasant for the patient. Multiple examples of sensations following administration were reported (Table 6), where the most common were residue in the mouth and need to drink water. Both related to characteristics of the formulation, which may be difficult to clear from the oral cavity. Some papers reported that these two sensations related to a specific *in vitro* parameter, i.e. granule size [25], particle size [27], [69], or type of co-administration vehicle [27] [69]. The amount of residue in the mouth was also predicted by PLS modelling based on formulation characteristics and disintegration behaviour [36].

In addition, sensations like numbness or astringency [62] [43] [46] [38] [41] [45] following administration, are more likely to be specific to the API rather than formulation attributes. For

example, greater coating thickness of API containing granules was related to reduced numbness [62].

In vivo-in vitro correlations reported

There are four major incentives to seek correlations between an *in vitro* method and sensory data for oral medicines: (i) to provide a tool for quality control; (ii) predict consumer preference (iii) understand processes underlying mouthfeel perception, as well as (iv) replace human panels for sensory evaluation and consequently reduce the costs of evaluation [70].

From a statistical point of view, establishing a meaningful relationship between *in vitro* and *in vivo* data can be done at several levels. First, by searching for simpler links, like agreement in the rank order of sensory assessment and instrumentally obtained values; such correlations can inform and direct further research. Establishing correlations between instrumental data and mouthfeel perception is challenging. While for the taste of solid oral dosage forms (beyond the scope of this review) correlations with *in vitro* data have already been established using several methods (e.g. e-Tongue [71,72] or BATA rat studies [73]), research on mouthfeel is limited. The most common correlations within sensory science that correlate food texture to instrumental methods are partial least squares regression which highlights liner relationships [74]. In this work linear relationships were evaluated to determine any likely correlations. However, there is scope to explore non-linear relationships and to develop principal component analysis maps of textures of oral medicines to better understand the correlation between in vitro and in vivo data [75].

In this literature review the majority of studies reported *in vitro in vivo* relationships using simple comparative methods. Additionally, some studies established whether the samples were statistically different (e.g. via t-test or Wilcoxon signed rank test, Tables 4-9). The relationship between human sensory perception was reported for two types of data: composition of the formulation (9 studies, refs: [28] [29] [30] [31] [33] [34] [53] [58] [63], and physical properties of the formulation (10 studies, ref: [25] [26] [27] [36] [39] [53] [58] [61] [62] [69].

Meaningful *in vitro in vivo* correlations were reported only for disintegration time (linear correlation coefficient), whereas no paper stated a numerical value of the correlation for other mouthfeel parameters. Two papers did apply advanced statistical tools to predict mouthfeel or palatability. Specifically, Casian et al [36] used PLS modelling to predict ODTs palatability based on (i) bespoke instrumental measure of disintegration profile and (ii) multiple formulation characteristics. While Lopez et al. [26] modelled perception of multiparticulate formulation grittiness using multiple linear regression. The prediction was based on multiparticulate formulation size, amount and viscosity of administration vehicle. The value of these approaches lies in the recognition of the complexity and multitude of factors that affect sensory perception.

The choice of excipient, like disintegrant/filler/softener/emulsifier, was found to affect the mouthfeel. Such information benefits the design of more palatable products, as it enables selection of appropriate excipients, for example, a disintegrant that provides the least rough ODT (e.g. use of croscarmellose sodium results in rougher ODT than one with crospovidone [31]).

Once the main formulation-based determinants of sensory perception are known, more complex testing and analytical methods can be performed to obtain meaningful correlations with *in vivo* data [70]. Robust correlations can increase understanding of the processes underlying sensory attributes that inform mouthfeel perception relating to oral pharmaceutical products. Finally, this knowledge can be leveraged to build a multifactorial model of sensory perception which can predict *in vivo* data based on *in vitro* input. The gaps in knowledge on key mouthfeel characteristics of formulations

coupled with the lack of application of advanced statistical correlations have limited the progression of *in vitro* methods to measure sensory properties of solid oral dosage forms.

There have been developments in *in vitro* methods to better replicate aspects of the anatomy and physiology of the mouth and thus provide better correlations to sensory data. For example, simpler adaptations to the texture analyser to measure force response to assess specific properties of medicines including adhesiveness of ODF [58]; hardness, elasticity, gumminess, adhesiveness of pastille [67]; elasticity of chewing gum [59]. More complex modifications of texture analyser were designed to measure disintegration profile of ODT, which controlled not only force response but also mimicked the temperature, humidity and saliva flow of the oral cavity [16] [76]. A further noteworthy example is a throat model that imitates the swallowing [69]. Such bespoke apparatuses are of value as they allow to observe oral processing or swallowing of oral dosage forms in mouth like conditions and understand processes underlying mouthfeel perception.

Standardisation of sensory analysis for pharmaceutical products

Achieving robust and applicable correlations between instrumental and human data is not possible without standardisation of methodology. Sensory analysis provides a more accurate measure of human perception compared to *in vitro* methods [77]. Refinement, development and harmonization of sensory methodologies within the pharmaceutical field have already been advocated [9].

The literature revealed that untrained (healthy) volunteers are typically used as study participants in pharmaceutical sensory assessment. This poses a significant difference from food sensory sciences, where trained panels are used to provide an objective description of sensory perception, while untrained participants (e.g. patients, consumers) to give a subjective hedonic opinion of the product [78]. Lack of training can result in subjective use of scales [79]. In the papers identified only one paper specified training of the panellists [26]. In this study, the panellists were trained with references for negative and positive controls to mark extreme ends of a grittiness scale for evaluation of multiparticulate formulation [26]. Admittedly, obtaining reference samples relevant for oral pharmaceutical products panel is a challenge. In pharmaceuticals, due to the infancy of the field, untrained participants are performing both sensory and hedonic evaluations within the same test.

The definition of the attribute under evaluation is a key factor in robust study design. A further difficulty in developing and standardizing sensory methodologies relates to the vast diversity of oral pharmaceutical products. Depending on the formulation, the residence time in the mouth, level of mastication and disintegration profile will differ. This poses a challenge to identify and select specific test methods and attributes for appropriate characterisation.

Standardization of terminology would facilitate clear communication between human sensory panel members, investigators and other scientists, and subsequently, increase the quality of pharmaceutical sensory studies. In addition, standardised tools would enable comparison across studies that would reduce the need for reference samples that are common in food science. In general, the terminology used within studies was correct, although some papers did not include definitions of measured attributes including the most basic terms including acceptability or palatability. In rare examples, the tool used to collate information on the evaluated mouthfeel attribute was confusing (e.g. *no gritty taste observed* [28] or scales that mixed sensory and hedonic terms (e.g. *gritty, acceptable, good, excellent*) [38] [46].

Conclusions

There is extensive literature that reports on the *in vitro* assessment of sensory attributes of solid oral medicines yet fewer that correlate *in vitro* to *in vivo* data.

Sensory attributes of oral formulations affect the acceptability of medicines and thus have an impact on patient safety, therapeutic outcomes and adherence. However, distinct differences in the key sensory attributes for a range of oral formulations means that separate considerations are required in the design of both *in vitro* and *in vivo* tests to better understand how these attributes affect patients overall hedonic response.

The value of instrumental measurements lies in their ability to generate high-throughput and objective, repeatable data. It is important to understand the relationship between instrumental and human data, and then apply this knowledge to speed up the development of more acceptable/palatable medicines. As sensory assessment within pharmaceutical science is in its infancy efforts should be focused on standardisation of testing strategies to maximise the translation of *in vitro* methodology and *in vivo* data whilst minimising the burden to participants.

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673 Figure and Table legends

674 *Figure 1: Flow diagram describing the literature review process.*

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677 *Table 1: Frequency of mouthfeel attributes by formulation type evaluated in the studies. (Note that*
678 *some studies reported multiple mouthfeel attributes and 2 studies reported multiple dosage forms).*
679 *ODT – orodispersible tablet, ODF – orodispersible film, MPs – multiparticulate formulation.*

680 *Table 2: In vitro and in vivo methodology used to assess grittiness/roughness. ODT – orodispersible*
681 *tablet, ODF – orodispersible film, SEM – scanning electron microscope, VAS – visual analogue scale,*
682 *API – active pharmaceutical ingredient; MPs – multiparticulate formulation *the direct relevance of*
683 *the measured parameter to grittiness/roughness is unclear.*

684 *Table 3: In vitro and in vivo methodology used to assess adhesiveness/cohesiveness and also*
685 *hardness/softness. ODT – orodispersible tablet, ODF – orodispersible film, SEM – scanning electron*
686 *microscope, API – active pharmaceutical ingredient; *the direct relevance of the measured*
687 *parameter to adhesiveness/cohesiveness or hardness/softness is unclear.*

688 *Table 4: In vitro and in vivo methodology used to assess general palatability/mouthfeel/acceptance.*
689 *ODT – orodispersible tablet, ODF – orodispersible film, MPs – multiparticulate formulation, SEM –*
690 *scanning electron microscope, API – active pharmaceutical ingredient, VAS – visual analogue scale,*
691 *PLS – partial least squares, *the direct relevance of the measured parameter to general*
692 *palatability/mouthfeel/acceptance is unclear.*

693 *Table 5: In vitro and in vivo methodology used to assess ease of swallowing/administration. ODT –*
694 *orodispersible tablet, ODF – orodispersible film,; SEM – scanning electron microscope, API – active*
695 *pharmaceutical ingredient, MPs – multiparticulate formulation, VAS – visual analogue scale; *the*
696 *direct relevance of the measured parameter to ease of swallowing/administration is unclear.*

697 *Table 6: In vitro and in vivo methodology used to assess sensation after administration. ODT –*
698 *orodispersible rating tablet, ODF – orodispersible film, MPs – multiparticulate formulation, VAS –*
699 *visual analogue scale; *the direct relevance of the measured parameter to sensation after*
700 *administration is unclear.*

701