Paediatric Formulation Development and Overcoming Taste-Masking Challenges

Subjects: Medicine, Research & Experimental

Contributor: Okhee Yoo , Britta S. von Ungern-Sternberg , Lee Yong Lim

Despite regulatory incentives in the United States and Europe to promote paediatric formulation development, progress is hampered by challenges including the need to address dose flexibility, swallowability, palatability, and the diverse physiological developmental stages encountered in the paediatric population. Peroral minitablets, microparticles, granules, liquid formulations, and scored chewable tablets have been proposed to address dose flexibility and provide ease of swallowability. However, given that one in four active pharmaceutical ingredients (APIs) have an intensely bitter taste and these formulations often result in drug interactions with taste receptors, palatability remains a significant challenge as young children are highly sensitive to bitter taste. This issue is especially prevalent for drugs required to be administered at high doses and frequent intervals, for example, anti-infectives, where the problem is further compounded by the high number (40%) of anti-infective APIs having an objectionable taste.

artificial neural networks (ANNs) paediatric drug formulations taste panels development machine learning

1. In Vitro Models

Surrogate in vitro drug dissolution assessment involves measuring the percentage of drug load released at specified time points from a formulation into simulated saliva. The use of traditional in vitro dissolution data to evaluate the taste acceptance of a medicinal product is simple, cost-effective, and convenient. However, this method is not able to provide the threshold concentration for bitterness detection of a drug in the target population. It also does not consider the size of the drug load in the formulation, and thus would not be able to differentiate taste differences generated by a 10% release of a 5 mg drug dose and a 10% release of a 500 mg drug dose. Additionally, the in vitro dissolution data do not account for variations in bitterness intensity between drugs or the role of excipients in modulating the organoleptic properties of the formulation. Furthermore, there is no published consensus on the methodology regarding sampling time points, type, volume, and agitation of the simulated saliva dissolution medium for in vitro drug dissolution studies to generate reliable surrogate taste scores [1][2].

E-tongue technology employs a range of flavour sensors to detect the five basic tastes: bitterness, sweetness, saltiness, sourness, and umami. These sensors operate by measuring changes in the membrane's chemical potential when immersed in a liquid medium, and the resulting signals are converted into a chemical pattern [3]. Lack of capacity to identify non-ionisable drugs in the sample medium is a constraint of the e-tongue technique [4].

This stands in contrast to the human tongue's ability to detect the taste of non-ionisable molecules [5]. Additionally, the e-tongue is limited to the evaluation of solutions. When the formulation under study is a solution, the sensors can be directly immersed in the formulation to measure its taste. For formulations that are not solutions, which account for the majority of new paediatric formulations, in vitro drug dissolution experiments have to be conducted and the e-tongue is employed to analyse the drug released from the formulation into the dissolution medium. Thus, the e-tongue is not capable of examining the role of excipients, nor measuring the texture and acceptability of the original formulation, resulting in its data not always able to be correlated with human taste data [6]. However, e-tongue technology has advanced in recent years, and biological electronic tongues (BioETs) now include bioactive materials such as receptors, cells, tissues, and other systems that aim to replicate the biological processes to more closely mimic human taste perception [7]. In one study, a BioET has been shown to provide a high degree of sensitivity and specificity to the taste of a variety of medium- and long-chain fatty acids, including lauric acid, linoleic acid, and docosahexaenoic acid [8]. Also, since BioETs are not restricted to only testing solution formulations, the influence of excipients on taste modification could potentially be detected using BioETs, in conjunction with artificial neural network (ANN) algorithms. Thus, while BioETs are a fascinating development, an in-depth knowledge of receptor cells that specialise in detecting distinct tastes or textures is crucial for determining overall taste acceptability using this technique. It is also yet to be validated against human gustatory data.

2. In Vivo Animal Models

The rodent-based brief-access taste aversion (BATA) assay has been proposed as an alternative to human taste panels and e-tongues for evaluating the palatability of APIs. The BATA method uses a lickometer to measure the frequency of licks made by mildly water-deprived rodents when presented with API tastant solutions at a range of concentrations, with low licking rates relative to the blank vehicle and/or water suggestive of aversive tastes [9]. While this method enables the generation of a comprehensive concentration–response curve for lick rates within a short timeframe and with minimal animal usage, a major concern is the ethical treatment of animals as they are unable to expel the aversive tastants. The experiments are performed under highly controlled environments as the animals' licking behaviour is readily affected by noise and light distractions. Rodents also typically exhibit heightened sensitivity to bitterness tastes compared to humans, which may not allow for direct data translation, and the necessity for ethical approvals may prolong product development timelines.

Fish or flies have also been used to evaluate the deterring effects of tastants [10][11], but there is no published method for the taste evaluation of medicinal formulations using these animal models. Taste scores generated using animal models have to be translated to provide equivalent human data, and while there are tools to translate taste scores from various non-human models to human equivalents [6][12], it is difficult to correlate an animal aversive response to the nuances of human taste data.

3. Optimising Taste Masking with Artificial Neural Networks

The implementation of the QbD approach to medicinal product development has led to the DoE being one of the most frequently utilised tools by pharmaceutical scientists [13]. However, the DoE, which relies on mathematical modelling, may not be as powerful a tool as artificial neural networks (ANNs), a machine learning approach inspired by the human brain. ANNs form the foundation of deep learning algorithms, and they have the potential to serve as valuable experimental tools for optimising and predicting desired product profiles. In contrast to DoE, ANNs can simultaneously model a large number of variables and establish intricate relationships between dependent and independent variables. Furthermore, ANNs can manage multiple outputs and model unstructured data, whereas the DoE mathematical models might be too simplistic to describe complex input-output relationships. In the field of pharmaceutical development, ANNs have been employed within the design space for predicting responses such as dissolution [14][15] and for optimising process parameters [16], but they have not yet been used to predict optimised formulation designs for an unpalatable API.

Moreover, with DoE, the initial design of a taste-masked paediatric formulation still largely depends on a process of trial and error, supported by the published literature, researcher expertise, and previous experiences, with consumer feedback becoming an increasingly significant component of this research process. Selecting a taste-masking formulation is a complex task, and there is as of yet no universal taste-masking technology that works for all APIs. There are numerous methods for masking the bitterness of APIs, including the addition of agents to mask taste (flavours and sweeteners) or inhibit the bitterness taste receptor, physical barrier methods (coating, granulation, emulsification, gelation), and chemical methods (tasteless prodrugs and ion-exchange complexation). The chosen method depends on multiple factors, such as the bitterness threshold concentration of the API, API–excipient interactions, physicochemical properties of the API, API dose to be administered, and the API load released from the formulation into the oral cavity. The first step in QbD involves designing a formulation that considers all the above factors. The research required for this can be resource-heavy, time-consuming, and at the same time uncertain, as the chosen formulation design may not successfully mask the API bitterness to an acceptable level, making it a costly endeavour.

The diversity of bitter molecules can make it challenging to predict whether a compound will taste bitter based on its chemical structure. However, researchers have developed machine learning classifiers to resolve this, although the bitter taste prediction remains limited to small molecules, bitter receptors for small molecules [17], and peptides [18]. For instance, BitterDB is a database of compounds reported to taste bitter to humans and some animals [17]. BitterPredict is a machine-trained model using data from BitterDB and non-bitter compounds from the literature, and claims to achieve high accuracy in classifying unknown compounds as tasting bitter or non-bitter [19]. Although useful for classifying large compound sets, this dichotomous classification is less helpful for medicinal formulation development where different taste-masking methods may be required depending on the level of API bitterness intensity. Another tool, BitterIntense, is a machine learning classifier that identifies molecules as “very bitter” or “not very bitter” based on chemical structure, boasting over 80% accuracy on several test sets [20]. More recently, a web-based database was created specifically for APIs prescribed for children [21]. This publicly available and electronically searchable database allows users to input the Simplified Molecular-Input Line-Entry System (SMILES) files of the main drug molecules to predict the taste of the resultant oral medicines [21]. VirtualTaste is yet another free-to-use web-based platform. Unlike the other databases, it is designed to predict three taste endpoints

—sweet, bitter, and sour—of individual compounds based on molecular fingerprinting determined by the machine learning algorithms built into the platform using published human data. The computational model claims to have an accuracy exceeding 88% and to provide a balance between specificity and sensitivity [22].

These databases are designed to predict the taste, in particular the bitterness, of individual compounds. They do not provide protocols for the taste assessment of complex admixtures of excipients and APIs typically present in medicinal formulations. However, advancements in knowledge and machine learning technologies over the past decade may make it possible for researchers to use machine learning to identify patterns in the relationship between molecules and effective taste-masking technologies. Machine learning can integrate numerous variables and uncover hidden correlations that contribute to specific taste experiences and may become proficient at discerning bitterness and its intensity in complex medicinal formulations. A critical requirement lies in having a dataset for the most effective technique for masking the bitterness of specific molecules. The use of machine learning to select formulation designs depends on acquiring knowledge from existing experimental data and previous experiences, and then making accurate predictions for new applications using the learned information from training datasets. Indispensable data for this training dataset include the concept of acceptance, which may well be provided by the net promoter score obtained from human taste panels, as outlined in the previous section. Validated and consistent acceptability scores from human taste panels together with the formulation details (excipients, manufacture processes, and taste-masking platform) are considered vital for advancing paediatric formulation development to the next level.

References

1. Keeley, A.; Teo, M.; Ali, Z.; Frost, J.; Ghimire, M.; Rajabi-Siahboomi, A.; Orlu, M.; Tuleu, C. In Vitro Dissolution Model Can Predict the in Vivo Taste Masking Performance of Coated Multiparticulates. Mol. Pharm. 2019, 16, 2095–2105.
2. Gittings, S.; Turnbull, N.; Roberts, C.J.; Gershkovich, P. Dissolution Methodology for Taste Masked Oral Dosage Forms. J. Control. Release Off. J. Control. Release Soc. 2014, 173, 32–42.
3. Guedes, M.D.V.; Marques, M.S.; Guedes, P.C.; Contri, R.V.; Kulkamp Guerreiro, I.C. The Use of Electronic Tongue and Sensory Panel on Taste Evaluation of Pediatric Medicines: A Systematic Review. Pharm. Dev. Technol. 2021, 26, 119–137.
4. Woertz, K.; Tissen, C.; Kleinebudde, P.; Breitkreutz, J. Taste Sensing Systems (Electronic Tongues) for Pharmaceutical Applications. Int. J. Pharm. 2011, 417, 256–271.
5. Choi, D.H.; Kim, N.A.; Nam, T.S.; Lee, S.; Jeong, S.H. Evaluation of Taste-Masking Effects of Pharmaceutical Sweeteners with an Electronic Tongue System. Drug Dev. Ind. Pharm. 2014, 40, 308–317.

6. Keating, A.V.; Soto, J.; Forbes, C.; Zhao, M.; Craig, D.Q.M.; Tuleu, C. Multi-Methodological Quantitative Taste Assessment of Anti-Tuberculosis Drugs to Support the Development of Palatable Paediatric Dosage Forms. Pharmaceutics 2020, 12, 369.
7. Tian, Y.; Wang, P.; Du, L.; Wu, C. Advances in Gustatory Biomimetic Biosensing Technologies: In Vitro and in Vivo Bioelectronic Tongue. TrAC Trends Anal. Chem. 2022, 157, 116778.
8. Lu, Y.; Huang, Y.; Li, S.; Zhang, Q.; Wu, J.; Xiong, Z.; Xiong, L.; Wan, Q.; Liu, Q. Fat Taste Detection with Odorant-Binding Proteins (OBPs) on Screen-Printed Electrodes Modified by Reduced Graphene Oxide. Sens. Actuators B Chem. 2017, 252, 973–982.
9. Soto, J.; Keeley, A.; Keating, A.V.; Mohamed-Ahmed, A.H.A.; Sheng, Y.; Winzenburg, G.; Turner, R.; Desset-Brèthes, S.; Orlu, M.; Tuleu, C. Rats Can Predict Aversiveness of Active Pharmaceutical Ingredients. Eur. J. Pharm. Biopharm. 2018, 133, 77–84.
10. Boyer, B.; Ernest, S.; Rosa, F. Egr-1 induction provides a genetic response to food aversion in zebrafish. Front. Behav. Neurosci. 2013, 7, 51.
11. Lvovskaya, S.; Smith, D.P. A Spoonful of Bitter Helps the Sugar-Response Go Down. Neuron 2013, 79, 612–614.
12. Clapham, D.; Bennett, J.; Cram, A.; Discihnger, A.; Inghelbrecht, S.; Pensé-Lhéritier, A.-M.; Ruiz, F.; Salunke, S.; Schiele, J.; Soto, J.; et al. Proposed Tool to Compare and Assess the Applicability of Taste Assessment Techniques for Pharmaceuticals. J. Pharm. Sci. 2022, 111, 1219–1223.
13. Cook, J.; Cruañes, M.T.; Gupta, M.; Riley, S.; Crison, J. Quality-by-Design: Are We There Yet? AAPS PharmSciTech 2014, 15, 140–148.
14. Obeid, S.; Madžarević, M.; Krkobabić, M.; Ibrić, S. Predicting Drug Release from Diazepam FDM Printed Tablets Using Deep Learning Approach: Influence of Process Parameters and Tablet Surface/Volume Ratio. Int. J. Pharm. 2021, 601, 120507.
15. Simões, M.F.; Silva, G.; Pinto, A.C.; Fonseca, M.; Silva, N.E.; Pinto, R.M.A.; Simões, S. Artificial Neural Networks Applied to Quality-by-Design: From Formulation Development to Clinical Outcome. Eur. J. Pharm. Biopharm. 2020, 152, 282–295.
16. Rodríguez-Dorado, R.; Landín, M.; Altai, A.; Russo, P.; Aquino, R.P.; Del Gaudio, P. A Novel Method for the Production of Core-Shell Microparticles by Inverse Gelation Optimized with Artificial Intelligent Tools. Int. J. Pharm. 2018, 538, 97–104.
17. Dagan-Wiener, A.; Di Pizio, A.; Nissim, I.; Bahia, M.S.; Dubovski, N.; Margulis, E.; Niv, M.Y. BitterDB: Taste Ligands and Receptors Database in 2019. Nucleic Acids Res. 2019, 47, D1179–D1185.
18. Charoenkwan, P.; Yana, J.; Schaduangrat, N.; Nantasenamat, C.; Hasan, M.M.; Shoombuatong, W. IBitter-SCM: Identification and Characterization of Bitter Peptides Using a Scoring Card

Method with Propensity Scores of Dipeptides. Genomics 2020, 112, 2813–2822.

19. Dagan-Wiener, A.; Nissim, I.; Ben Abu, N.; Borgonovo, G.; Bassoli, A.; Niv, M.Y. Bitter or Not? BitterPredict, a Tool for Predicting Taste from Chemical Structure. Sci. Rep. 2017, 7, 12074.
20. Margulis, E.; Dagan-Wiener, A.; Ives, R.S.; Jaffari, S.; Siems, K.; Niv, M.Y. Intense Bitterness of Molecules: Machine Learning for Expediting Drug Discovery. Comput. Struct. Biotechnol. J. 2021, 19, 568–576.
21. Bai, G.; Wu, T.; Zhao, L.; Wang, X.; Li, S.; Ni, X. CBDPS 1.0: A Python GUI Application for Machine Learning Models to Predict Bitter-Tasting Children's Oral Medicines. Chem. Pharm. Bull. 2021, 69, 989–994.
22. Fritz, F.; Preissner, R.; Banerjee, P. VirtualTaste: A Web Server for the Prediction of Organoleptic Properties of Chemical Compounds. Nucleic Acids Res. 2021, 49, W679–W684.