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REVIEW ARTICLE

Size and Taste Matters: Recent Progress in the Development of Age-Appropriate Medicines for Children

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Abstract Drug therapy for children is one of the cornerstone developments that have sharply reduced childhood mortality. Despite this, many challenges remain in ensuring that children receive safe and effective drug therapy. There are unique issues in treating children with oral medication relating to development, existing formulations and medication acceptability. Medication acceptability in children is complex relating to a wide range of factors, including drug palatability. Over the past decade there has been an increasing interest in and research as to how to improve and enhance child-specific drug formulations including the development of specific instruments for assessing drug palatability in children and new approaches to teaching medication literacy to families. Approaches to enhancing drug acceptability have also included organoleptic (taste masking) strategies as well as the creation of a number of innovative taste-blocking strategies and new technologies for formulation preparation. Polymer coating, microencapsulation and heat melt technologies have resulted in drug formulations that are now being assessed in children while soft melt and gel formulations are now commonly used. Mini-tablets offer the potential of using solid delivery systems in even very young infants. This work has resulted in a number of highly promising developments that are being evaluated for clinical use as well as providing insights into new directions in pursuit of the common goal of effective and safe drug therapy for children. On-going challenges include the need for drug regulatory agencies to work closely with drug regulatory agencies in facilitating innovation in formulation design and approval.

Key Points for Decision Makers

Administering medication to children is difficult and often related to drug formulation.

There have been major advances in this area over the past two decades in terms of assessment of drug acceptability in children and in novel formulations.

Moving forward will require partnership between investigators, industry and drug regulators.

1 Children and Medication

Medications—in terms of specific therapy—are key cornerstones of contemporary healthcare, and along with vaccination, improved living conditions, better nutrition and public sanitation, have been revolutionary in sharply reducing childhood mortality—which has been between one-quarter and one-third of all children for most of human history—to the current very low levels [1, 2]. As an example, while the mortality rate for American and Canadian children was 25% in the early twentieth century, the current mortality rate for children up to age 5 is approximately 0.6%, primarily related to issues linked to birth and congenital anomalies.

Medication use in children is common. When our group studied a cohort of one million children in Canada for

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1 year, they made three key observations. First, medication use was common—on average four prescriptions per child per year [3]. Second, medication use involved a wide range of medications—in fact, more than 1200 different therapeutic agents from a number of therapeutic classes. Finally, drug use was not distributed equally. Most children received either no or one prescription over the year, while 20% of the children accounted for 70% of drug use, primarily children with serious diseases such as cancer, and chronic diseases such as asthma or epilepsy [3]. Studies in other jurisdictions have demonstrated similar findings—an FDA study following drug use in US children found that, in 2010, US children received on average 3.5 prescriptions per year [4].

There are many factors that impact on optimal drug therapy for children. Some of these factors include key developmental tenets. Changes in drug disposition have been associated with therapeutic tragedies in children, notably infants [2]. Over the past five decades, the ontogeny of drug disposition has become much clearer, notably for pre-term and term infants [5, 6]. This knowledge has, in turn, informed therapeutic decision making, although much remains to be discovered [6, 7]. The risk of adverse drug reaction is also an important consideration, and adverse drug reactions in children have been a major driver for many of the regulatory changes that drive the current drug approval system [8].

Historical challenges to drug therapy for children included regulatory issues. The 1962 Kefauver-Harris amendments to the US Food and Drugs legislation, made in response to the thalidomide tragedy, that were intended to improve drug therapy for humans, including children, in many cases had the opposite effect [2, 9, 10]. This led to the increasing use of off-label prescribing, rendering children "therapeutic orphans", as coined by Dr. Henry Shirkey in 1968. Over the past years several initiatives have been put into place to enhance and expand drug research—and appropriate labeling—for drug use in children [11–14].

These could be considered challenges at the strategic level. There are a series of other very distinct challenges at the tactical level related to the pragmatic administration of safe and effective drugs for children. Some of these issues are developmental and most relate to drug formulations. This review will consider drug acceptability in children and the way in which issues in drug acceptability can be addressed.

2 Taste and Swallowing

Humans are born as obligate milk feeders, and the ability to process and swallow a solid bolus occurs during development. Swallowing itself is a complex process. It begins in utero with the swallowing of amniotic fluid [15, 16]. The mechanics of swallowing involve an intricate interplay between oral, lingual, laryngeal and esophageal muscles and supporting soft tissue and skeletal structures, with sensory inputs from the trigeminal nerve informing outputs via its maxillary and mandibular branches as well as outputs from the facial nerve, the glossopharyngeal nerve, the vagus nerve and the hypoglossal nerve [15]. These inputs and outputs are coordinated in the hindbrain with some contribution from the descending forebrain. The integrated process of feeding that these processes control involves ingestion of food, chewing and salivary processing, accumulation of a bolus and oropharyngeal transport and swallowing, accomplished by sequential and synchronous neural activation and inhibition [16]. As can be imagined, this is a complex process that takes some time and effort to develop and which is subject to perturbation.

The ability of children to swallow a bolus of solid food begins with the ability of infants to use their tongue to move food to the back of the mouth, typically at about 4–5 months of age for full term infants [17]. As dentition comes in over the first year of life, children acquire the ability to chew and to swallow a larger bolus of food [17]. The implication of this for medication is that the vast majority of medications are given orally, and the vast majority of oral medications are dispensed in a solid dosing form such as tablets or capsules. The pragmatic issue is that there are certain ages below which children are very unlikely to be able to tolerate solid dosage forms. As noted above, most children do not commonly take medications, and for these children it is uncommon for them to be able to tolerate conventional solid dosage forms until ages 8–10 years. Among the 20% of children who take medications frequently, it is uncommon for children to be able to tolerate conventional solid dosage forms below the age of 5 years [18]. It should be noted that this is not a unique problem for children, as up to 10% of adults cannot tolerate solid dosage forms for a number of reasons beyond the scope of this review.

The reasons that children have difficulty with oral drug dosing include developmental issues related to swallowing, available dosing forms and palatability. Palatability is a sensation dependent on a number of factors, notably taste. Taste is a sensation produced by the interaction of an ingested substance with the taste buds, specialized structures present on the various papillae on the tongue that contain taste receptor cells [19]. Ingested substances access these cells via taste pores that are projections of microvilli from the taste receptor cells; activation of taste receptors, which are G-protein coupled receptors, are then signaled via the facial nerve [20].

Palatability in turn is a hedonic reward that is a complex construct combining taste, texture, smell and individual

preferences and experiences to determine the degree of pleasure or displeasure that is associated with ingestion of a substance. For children, both smell and texture are important parts of palatability. In addition to age-specific factors, palatability may vary with the state of the individual and is also subject to previous experiences as well as cultural context.

3 Medication Acceptability for Children

The traditional approach to the problem of children being unable to swallow solid dosage forms has been to change the dosage form. This has included alternate delivery systems, the development of liquid dosage forms and the alteration of existing dosage forms [21].

The decision to use an alternate delivery system is attractive but limited to a relatively small number of therapeutic classes. The use of topical preparations in ophthalmic care—drops and ointments—has been common for many years [22]. Similarly, the use of topical preparations for dermatologic problems is an obvious route that has in fact been used for many centuries [23]. The use of drug delivery patches is possible, but this approach is much more commonly used in adults than in children for a number of reasons related to therapeutic indications and concern over patch removal. Over the past four decades there has been an increasing use of inhaled medications for conditions such as asthma, to the point at which this route is now considered the route of choice for these indications [24]. That being said, while these delivery methods work very well for these specific classes of disease, most drugs for children still are administered orally. In this case, the two alternate approaches have been used.

The development of a liquid dosing form has been a classical approach to this problem, most commonly used for antibiotics [25]. This has largely been driven by frequency of use of antibiotics for children and these preparations have been available for many years. For those drugs that are not available in liquid form, a common approach has been to crush and administer the medications in, for example, apple sauce, or with other flavoring agents.

While these approaches have been used for many years, they have not been problem free. Liquid preparations of medications are typically more expensive on a per-dose basis than their solid dosage form equivalents. Many preparations are sold as dry powders and must be re-constituted prior to use, which may require specialized personnel and as well require a supply of clean water, which may be an issue in the developing world. Once prepared, most liquid medications have a much shorter shelf life than their solid dosage form equivalents, and often require refrigeration—again an issue in the developing world, where most of the world's children live. As well, the dosage range may be somewhat limited by the available formulations. Finally, the ability to administer an accurate dose is markedly more problematic for a liquid than a solid dosage form. Best practice is to use a measuring device—such as an oral syringe—to ensure that the prescribed dose is accurately administered, notably as alternatives such as kitchen spoons have been demonstrated to vary very widely in the volume they contain.

3.1 Acceptability, Taste and Palatability

Then there is the question of acceptability. Acceptability is the degree to which a patient—or in case of a young child, their caregiver—is able to dispense the medication in the manner recommended by the prescriber [26]. This is a very complex concept involving a number of factors, some inter-related and some distinctly different (Fig. 1). For oral medications, the impacting factors can be palatability, ability to swallow the medication, dosing frequency and need for concurrent activity during or prior to dosing.

The issue of dosing interval is important for all patients, but especially for children. Once in school, it can be difficult for children to receive medication that is required more often than twice a day. This is an issue for adolescents too, as social pressures to conform to the norm of their peers, can make adolescents less compliant than younger children. This phenomenon can be seen frequently in circumstances such as diabetes care, when compliance (as assessed by glucose control) often deteriorates dramatically when insulin administration transitions from parent to adolescent. Adapting medication regimens to the adolescent life style—and to adolescent expectations—is a challenge for patients and healthcare providers.

For young children, taste and palatability are key factors. Most antibiotics—in fact, most drugs in general—are

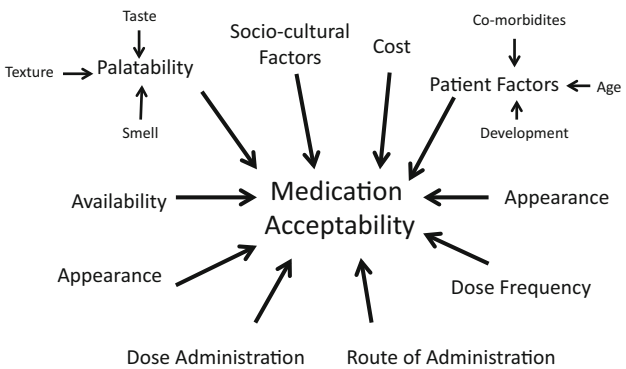

Fig. 1 The complex case of medicine acceptability for children. The many factors impacting on the way in which children and families are able to take medications in the dose and manner prescribed. Derived from Rieder [2], Baguley et al [25], Zajicek et al [27], Tuleu et al [51] and Mistry et al [58]

small molecules that are by their nature bitter. In many cases it is difficult to mask this taste. Also, most antibiotic liquid preparations are suspensions, not solutions—and particle size may impact on issues such as texture. Finally, in terms of regulation there is no consistent guideline on what is an acceptable dosage form for children nor what are acceptable ingredients and taste standards [27].

3.2 Practical Issues in Giving Medication to Children

These problems can have significant consequences for therapy. Parents frequently relate tales of significant difficulty in administering medication to their children. This can have significant consequences in terms of compliance. A number of studies in countries ranging from the Middle East to Japan have demonstrated that children often do not complete courses of therapy or have sub-optimal compliance based on difficulty in administering medication to children [25, 28–30]. Among Canadian children being treated for HIV infection, we demonstrated that up to one-third were receiving significantly less antiviral therapy than required due to palatability issues [29]. For some disorders, this can result in extreme measures; an example is in children with urea cycle disorders where sodium phenylbutyrate is an essential medication but is sufficiently unpleasant that some of these children have required gastric tube insertion for medication delivery [31]. The consequences can extend beyond the patient; children on maintenance therapy for leukemia for most protocols require a daily oral dose of 6-mercaptopurine, which is only available in a tablet formulation. There are numerous parent blogs describing how to grind the tablets in the kitchen, which has the dual consequences of a potentially inadequate dose for the child while exposing other members of the family to an active chemotherapeutic agent [27]. Finally, no consideration of palatability for medication can fail to consider the impact of the Elixir of Sulfanilamide tragedy of 1937, when more than 100 patients, mostly children, died of renal failure as a consequence of the use of diethylene glycol as a solvent for sulfanilamide to develop a liquid dosing form for sulfonamides and to improve palatability [32]. The creation and evolution of the current drug regulatory system used by most developed nations is a direct consequence of this tragic outcome [1, 2].

One of the first challenges faced in addressing palatability is measurement. Historically, the palatability of liquid medications was assessed among adult volunteers. The frequently cited aphorism that "children are not small adults" is especially true in the area of taste. The density of the papillae housing taste receptor cells changes over childhood, with younger children having papillae concentration that tends to favor sweeter tastes [33, 34]. This changes as children move into adolescence and the tendency to favor sweets declines. As well, young children appear to change their taste preferences with repeated exposure, which is not the case for adults [34].

Early work with medication palatability explored this issue with liquid antibiotic preparations. One of the first was how to create a valid instrument to measure palatability, a problem that was addressed by the use of a facial hedonic scale [35, 36].

A Canadian study on the palatability of liquid cloxacillin, which is known for its bad taste, found that 90% of healthy children tested rated it as the worst tasting antibiotic ($p > 0.001$) (Fig. 2) [35].

A number of investigators have used this approach to study the palatability of different medications, ranging from activated charcoal to corticosteroids to anti-viral drugs [37–41]. These studies have been useful in our understanding of the palatability of various formulations and in helping the design of alternative formulations. The facial hedonic scale appears to be a valid and useful instrument for assessment of palatability in children aged ≥ 5 years. However, there are several limitations to this approach. First, to use the facial hedonic scale the children must have at least some concept of numeracy; that is to say, they need to appreciate that five is greater than one. This appear to be present fairly predictably by ages 4–5, limiting the use of this instrument to children this age and older. The second issue relates to ethics [42–45]. Initial studies were conducted in the 1990s using healthy child volunteers [35, 36]. At that time, it was acceptable in Canada to give a healthy child with no allergic history a single dose of an antibiotic under the principle that research involving healthy children should involve no more risk than the usual risk of everyday life. Subsequently there has been a vigorous debate—with interesting cross-Atlantic differences in perspective—as to what exactly the usual risk of everyday life constitutes. There has been a school of

	Cloxacillin	Cephalexin	Erythromycin	Fusidic Acid
Taste Score (mm)	140 ± 180	650 ± 270	680 ± 300	630 ± 240

Fig. 2 Facial Hedonic Scale for assessment of palatability. Children administered the scale were asked via a predetermined script whether they liked the medication a lot, a little or didn't care, or whether they disliked it a lot or a little. While asking the faces were referenced for each point. Matsui et al [36]

thought that any risk was unacceptable, a nihilistic approach that has subsequently been refined to the concept that children should be protected by research, not from research [46]. Applying this to research on palatability, most Research Ethics Boards in North America and Europe would view palatability testing as acceptable if the child would be receiving the medication. Thus, more recent studies have conducted this work using children for whom a medication has been prescribed and have assessed the palatability of the medication prescribed plus therapeutic alternates [40].

4 Approaches to Drug Acceptability for Children

Historically, issues such as palatability have not been a consideration by regulatory agencies or in the development of guidelines [25]. However, the increasing interest in pediatric formulations by parents, healthcare providers and investigators has been accompanied by interest in this area by drug regulatory authorities [27, 36, 47–55]. Both the American Food and Drug Administration (FDA) and the European Union European Medications Agency (EMA) have had workshops exploring best practices in this area [49, 50]. After several decades of relatively little activity, there have been several new liquid formulations developed over the past 10 years. Recent examples include a liquid formulation for valaciclovir and a novel liquid preparation of prednisone [42, 56]. These two studies illustrate how the field of formulation design for children has changed over the past few decades. In both cases formal palatability assessments were undertaken. In the case of the valaciclovir study, in addition to testing in vivo with children who had taken valaciclovir, the investigators explored the use of an "electronic tongue", a sensor using eight separate components to assess a range of tastes [42]. In the case of the corticosteroid study, the investigators studied how an old drug—prednisone, known to taste badly—could be administered in an alternate form, as prednisone-loaded microspheres [56]. When this preparation was assessed by a panel of adolescent and young adult volunteers, it was found that this approach essentially masked the unpleasant taste of prednisone [56].

4.1 Taste Masking

While this approach has been useful for liquid medications, there are many problems with the historical approach to medications for which there are no liquid preparations [27, 57–68]. Converting a solid dosage form to a powder or other more easily swallowed dosage form introduces a number of potential problems. Most solid medications are not designed to be crushed—quite the contrary, they are usually designed to be crush-resistant and hence may be difficult to pulverize. When crushed, if care is not taken, part of the dose may be lost. If a crushed medication is mixed with food, it is possible that absorption may be impacted by concurrent administration with food. Returning to the issue of dose, mixing a crushed drug with food mandates consuming the entire food portion that the drug is mixed with. Finally, crushing a medication eliminates any formulation designs that are intended for extended release—whether a polymer-dispersed matrix, a modified dissolution strategy, or an osmotic approach.

As well, even mixing crushed medications with food may not mask the very bitter taste of many drugs; in some cases, drugs are so bitter that the use of crushed medications is very unlikely to be practical for extended periods of therapy [61]. In response to these concerns and recognizing the limitations of conventional liquid medications, a number of novel formulation alternatives have been explored. Some of these involve reconsideration of solid dosage forms and some are markedly different in approach.

A classical approach to dealing with adverse taste—including adverse taste of liquid medications—has been taste masking. This involves adding a different taste to improve the palatability of the product. Initially this was most commonly done simply with syrup, which is essentially a mixture of sugar and water with or without other flavoring agents. A number of different approaches have been developed to provide alternative taste masking strategies (Table 1) [62–64]. These strategies take the approach of masking or hiding a bitter drug flavor (e.g. putting the drug into yogurt) from the hands of the patient or caregiver and moving this to the pharmacy or the drug manufacturer [62–67]. There are essentially two strategic directions. The first involves altering the taste of the drug using flavoring agents (Table 1); there are a wide range of these agents commercially available, the field having moved significantly beyond simple syrup. This approach has been used for some time in drug manufacture and now is commonly employed at the level of dispensing pharmacies. The second involves the creation of a physical barrier between the drug and the taste buds (Table 1); there are several possible approaches. These range from polymer coating and microencapsulation—both of which have been used for some time in drug manufacturing—to newer techniques such as hot melt extrusion [62–64] (Fig. 3). As part of this approach, it is also important to consider if an alternate form of the drug, such as a salt, might be more palatable or more suited for the development of a different dosing form [59, 69].

When drugs do not undergo significant first-pass metabolism one possible approach is to use an intravenous preparation orally. This is not without issues; typically, intravenous drugs are even more bitter than might be

Table 1 Taste masking strategies

Taste alteration strategies
Organoleptic approaches
Addition of flavoring agents such as sweeteners or flavors
Taste barrier strategies
Polymer coating
Provision of a physical barrier to coat the drug by single or sequential coating
Spray drying
Provision of a physical barrier when the drug and a polymer are coated by spray drying
Microencapsulation
Encapsulation of the drug using coatings such as polymeric membranes
Complexation
Formation of inclusion complexes of the drug with compounds such as cyclodextrins or ion exchange resins
Hot melt extrusion
Heating of the drug and other ingredients to create taste-masked granules

Derived from Ayenew et al. [63]

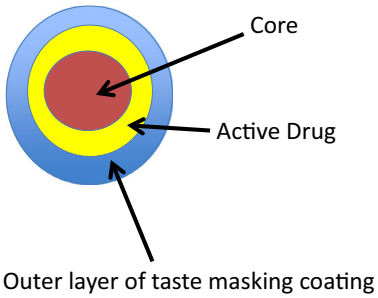

Fig. 3 Encapsulation as a strategy for taste masking

expected, and taste masking with a sweet tasting agent may still not provide a palatable solution. As well, intravenous drugs are typically more expensive than their oral counterparts. Nonetheless, this approach has been used successfully, on occasion. A recent study exploring the use of an intravenous preparation of ondansetron given orally with flavoring demonstrated acceptable palatability (3.2 out of 5 using a facial hedonic scale) as well as good absorption, as assessed by serum drug concentrations [70]. This is useful in settings where intravenous ondansetron might be available but there may be no approved oral formulations available. In cases where there may be no good options, co-administration with food may be necessary. In this context it will be important to determine not only the potential impact on drug efficacy (given possible changes in drug absorption) as well as to which foods might be preferable. An appreciation of the potential effects of co-administered food on key determinants of drug absorption—such as gastric motility and potential effects on transporters—is important in considering this strategy [71]. A study explored this option with the oral iron chelator deferasirox, which demonstrated increased gastrointestinal tolerability as well as an acceptable pharmacokinetic profile [41]. This also points to the feasibility of taste-masking assessments for solid drug dosage forms [68]. While several approaches have been described, these do not often use real-world conditions relating to variables such as altered volumes of saliva, oral dose dwell time in the oral cavity and timing of evaluations [68].

The frequent use of taste-masking technologies in clinical practice has created practical challenges in implementation. When giving instructions to parents, there can be significant changes in literacy that can lead to misinterpretations and possible medication errors. Emerging work in medical literacy has demonstrated that the use of pictograms can substantially increase parental understanding of medication administration techniques to be used for their children [65].

4.2 Taste-Blocking Approaches

Another approach is to consider whether an alternate solid dosage form might be suitable. As noted above, techniques such as micro-encapsulation can be used to render unpalatable drugs more acceptable. A recent example is the development of a microencapsulated form of hydrocortisone for the therapy in infants with adrenal insufficiency [72]. The study demonstrated that the product was well evaluated by parents; in terms of palatability, a surrogate outcome for infants—most of the children in the study—was by parental evaluation of ease of administration, which, given the constraints of palatability evaluation in children, seems a very reasonable approach [32]. Similarly, using β-cyclodextrin and a cherry/sucralose flavor system markedly improved the palatability of cetirizine. This

finding was demonstrated by both sensor and human volunteer assessments [73]. These approaches are very promising but require careful and thoughtful design, not only in terms of palatability but also in terms of biopharmaceutics [74].

An alternate dosing form that is especially attractive for children is the use of mini-tablets. While conventional capsules and tablets often measure a diameter in the 10–20 mm range, mini-tablets are very small, typically 1–2 mm in diameter [76–78) (Fig. 4). Mini-tablets offer an interesting alternate not only to larger solid dosage forms but also to conventional liquid medications. In terms of how low the age envelope can be pushed, the effective use of mini-tablets has been demonstrated in children as young as 6 months, and even in pilot work in neonates [75, 76]. While tablets this small can provide an intimidating challenge for parents, they do provide an alternate route for therapy for children, that avoids many of the previously cited issues with liquid formulations, notably when used in uncoated rapid-release formulations [77].

4.3 Soft Gel and Melt Technology

Another alternate to liquid medication is the use of rapid dissolving or melt technology [77, 78]. This has been used most commonly to develop soft gel or melt technology for use with non-prescription medications such as vitamins, ibuprofen or acetaminophen, likely related in part to wider dosage tolerances and also to the very large market for these products (paracetamol). Efficacy and safety have been demonstrated for these formulations and they appear to be quite popular with patients. In terms of soft gel formulations, there is an emerging very large market for adult nutritional products such as vitamins, using this formulation design.

The desire to enhance acceptability of drugs for children has extended to the rapidly growing use of psychoactive drugs in children and adolescents. While therapy for attention-deficit-hyperactivity disorder (ADHD) has used with both conventional and sustained-release formulations for some time, over the past several years a number of very novel formulations (including osmotic delivery systems, liquid formulations and patches) have been studied for use in children and adolescents [79]. Challenges that arise when developing formulations for these indications include the need for sustained-release formulations; problematic when using liquid medications, but an issue that can be addressed by careful engineering of technologies such as micro-encapsulated particles.

With respect to adolescents, the key factor to ensure acceptability is ensuring that medication administration is compatible with adolescent life style. Ensuring once or at most twice a day administration is important. There may be an advantage in long-acting or depot drug administration in certain circumstances.

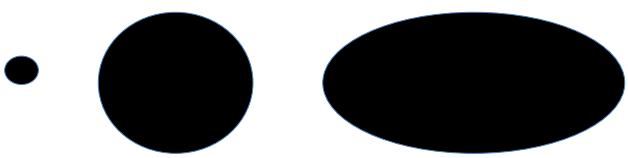

Fig. 4 Relative differences in size between a 1 mm diameter mini-pellet, a 5 mm tablet, and a 10 mm capsule

5 Future Directions

The area of medication acceptability for children has moved dramatically over the past two decades, and there are good reasons to believe that this progress will continue [80, 81].

As noted above, many drugs are by their nature bitter. However, this is a somewhat subjective assessment that is usually made, post-hoc, fairly late in the drug development process after the molecule has been assessed for efficacy and safety using a number of screening panels and validation approaches. Given the cost of drug development, efficacy and safety are now increasingly being modeled in silico prior to conducting wet laboratory studies. Given our understanding of existing compounds and the development of databases that incorporate this information in searchable formats, there has been interesting work in applying computational approaches to predict drug bitterness in silico [82]. This approach is still investigational but is clearly very promising.

An area that is under active investigation is in taste evaluation. As noted above, instruments have been developed that can reliably evaluate taste and palatability in children aged 5 years and above. However, there is a need for methods to be used during earlier stages of drug development to evaluate panels of various formulations without needing to conduct these trials in volunteers. Given the ethical issues outlined above, this is a pragmatic need to provide at least an initial screen for formulations that can then be validated in the populations in question. As well, there are no reliable validated methods available to assess palatability in younger children. One approach that is being investigated is an "electronic tongue". This is essentially a battery of sensors that evaluate various aspects of taste in solutions that are then integrated to produce a final output. This has been used experimentally in several studies with promising results [24, 73]. Given the contribution of texture and smell to palatability, clearly there are limitations to this currently, but this remains an area of active research [42, 73].

A novel approach to taste masking is to bypass the taste system altogether. Given that taste is, simply put, a receptor-driven phenomenon, then one potential strategy is to create ligands that block taste receptors. Another potential approach is to block the taste signal cascade. The ability to rapidly and reversibly inhibit taste receptors or the taste cascade would offer an entirely new approach to the problem of palatability [68, 83].

Once a promising candidate molecule has been identified and potentially evaluated in silico, there are an increasing number of options for drug formulation. One of the first decisions is which dosage form strategy should be pursued. If the decision is to pursue an oral formulation design, there are an increasing variety of potential formulation strategies. These include the various taste-masking strategies discussed above as well as fundamental differences in formulations such as micro-encapsulation, mini-tablets or gel or melt technology [77, 83–85]. In addition to the challenges of drug design, attention must be paid to the use of novel excipients by innovators, industry and drug regulatory agencies [69]. Other approaches under study include the use of micro-needles, which are micron-sized projections extending from one side of a patch; medications can be delivered via these very small needles, possibly in combination with a hydrogel to enhance skin permeability [86].

The development of appropriate formulations for children also requires a very close working relationship between industry and drug regulatory agencies. There are significant tensions in this relationship when a drug formulation used in studies conducted as part of drug development differs from the final proposed formulation for marketing. Groups such as the European Paediatric Formulations Initiative (http://www.eupfi.org) are working to address these issues to facilitate more harmonious development of child-friendly formulations.

In addition to technologies that change the formulation, approaches are being pursued that enhance the ability of children to swallow existing solid formulations. One such approach uses the Pill Glide™, a flavored throat spray intended to be given prior to taking a solid medication. A pilot study from the UK has shown very positive results in ten children transitioning from liquid to solid medications [87]. The generalizability and long-term impacts of this approach need to be studied, but it is a promising new direction.

In the era of precision medicine, pharmacogenomics is extending to many areas, and palatability is one of them. TAS2R38, a gene coding one of the bitter taste receptors, is known to have at least three single nucleotide polymorphisms coding for variants that are major determinants of bitter taste [88]. Polymorphisms in bitter-taste receptors have been demonstrated to be important in bitter sensations to sweeteners, and there is great potential in applying this work to medications [88, 89]. Much remains unexplored, including the clinical relevance of differences in single nucleotide polymorphisms and how these are distributed in ethnically heterogenous populations. As our knowledge of the genetics and biology of taste evolve, it is possible that we will be able to apply these findings to drug acceptability in the way we are beginning to apply them in drug safety [90].

The final and perhaps most important considerations are the factors that impact on children, their families and their healthcare providers in terms of medicine acceptability [91–94]. The common goal of families, healthcare providers, regulatory agencies and industry is that children receive effective and safe drug therapy. A clear and comprehensive understanding of the many factors that impact on acceptability and the degree to which patients, their families and their healthcare providers can and will accept changes in formulation and drug delivery is the key foundation in moving the exciting developments of the past decade—and of the decade to come—into routine clinical use.

Compliance with Ethical Standards

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