REVIEW ARTICLE

Navigating the Complexities of Pediatric Formulation Development and Challenges

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Abstract

The formulation of pediatric dosage forms continues to be a great challenge due to significant differences in profiles of children and adults in terms of physiology, anatomy, and development. Buccal drug delivery systems have been developed as an alternative to oral drug delivery when oral dosage forms are not suitable and have several benefits to be noted, including better patient compliance, ease of administration, avoidance of first-pass metabolism, and better bioavailability. However, excipients frequently used in adults' formulations are not suitable in children and can present potential safety and efficacy issues. Hence, the physiology of the pediatric group, as well as the suitability of excipients, must be carefully considered in the successful development of pediatric buccal dosage forms. Going forward, formulation strategies should be directed at the identification and evaluation of safe pediatric excipients, the incorporation of novel drug delivery technologies for the precise and individual delivery of drugs, and the enhanced cooperation between regulatory agencies, researchers, and the pharmaceutical industry. Such efforts are necessary to fill in existing therapeutic voids to enhance health care in children.

Key words: Biological, buccal, dosage forms, excipients, formulation design, oral, pediatric

INTRODUCTION

Pediatric patients are frequently treated with off-label medications intended for adults through custom compounding; both approaches are considered suboptimal due to the absence of established effectiveness and safety for this specific population. This issue is especially complicated for infants and toddlers, as well as for those with uncommon or long-term disorders and acute illnesses. Many new medications are authorized for adult use despite the lack of adequate data on their effects in pediatric patients. Consequently, healthcare providers are frequently compelled to prescribe off-label, relying on inadequately defined dosing guidelines. In the United States, nearly half of all medications are not labeled for pediatric use.[1] More than one-third (36.7%) of hospitalizations for children involve the use of analgesics off-label, which have not been approved for this age group.[2]

The "Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)" were introduced to promote greater clinical studies of children's medications.[3] These regulations primarily aim to increase the number of drugs that are clinically tested for pediatric use and ensure that they are available on the market with suitable formulations and dosing. Beyond encouraging the development of medications for children, and also specific factors for children that need to be considered.

This has led to many therapeutic medications remaining unavailable in pediatric -friendly formulations. Although the legislative provisions initiated through the best pharmaceuticals for children act (BPCA) and pediatric research equity act (PREA) have advanced pediatric research and labeling for newer drugs, mandates often do not apply to existing medications. Older medications might, therefore, not be covered under these measures. Pediatric formulations, especially formulations for very young infants,

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are among the most difficult to develop. Information about the acceptability of different types of formulation, such as "administration volume, size of dosage form, flavor, and toxicological profile of formulation excipients related to the age and developmental stage, are relatively scarce." Other factors associated with failure in pediatric studies are dosing, nature of pathophysiology, research design, and inactive treatment responses. This, therefore, calls for the knowledge of the causes of failure in these studies to be adequately applied in making better strategies for designing successful pediatric trials later. According to Wharton *et al*., 189 products granted pediatric exclusivity between 1998 and 2012 could not establish pediatric labeling. This has boasting them with a failure rate of 42%.[4] Pediatric preparations are typically administered orally, and products intended for this use are commonly provided as powders to be reconstituted. However, reconstitution requires deionized water and, in some cases, specific storage conditions like refrigeration – requirements that are not always feasible to meet.

Most liquids are unpalatable and difficult to swallow when in powder form. The ability of children to swallow is not that of adults; hence, it is particularly hard for pediatric patients to take in solid dosage forms. In general, most children cannot safely swallow more than 10 mm-sized solid capsules and tablets safely. Second, taste is also another factor that children will not tolerate and can refuse treatment regardless of the tablet size if it tastes bad. For instance, clarithromycin is very bitter and less palatable as compared to other drugs in the same category of antibiotics.[5] It will thus follow that other drugs with such bad tastes may lead to complications in terms of scheduling and timing doses for consumption. The rectal route is less frequently used than the oral route, but can be a substitute when the use of the oral route will likely result in nausea or vomiting. The common forms used in the rectal route include suppositories, creams, enemas, and ointments, but those are often cumbersome to administer to a child. Whenever an emergency occurs or the oral route is impossible, the parenteral route can also be used because the onset is fast. Although the parenteral route offers the above advantage, several limitations prevail, such as the requirement of a trained professional for its administration, the invasive nature of the procedure involved, potential infections transmitted through blood-borne infection, and the hazards of injections that may lead to pain or injury.[6] While clinicians may prefer parenteral administration due to the short onset time and high bioavailability of drugs, the associated patient acceptability, sterility requirements, and need for adequately trained medical personnel raise specific challenges. Given the above challenges, the buccal route becomes the more attractive route.

In specific conditions, the buccal route could be very suitable, including during seizure time and in patients for whom oral, rectal, or parenteral routes may not be appropriate or possible. Speedy and effective relief of pain is key for most pediatric cancer patients who experience severe breakthrough pain. In such scenarios, the oral route is not ideal due to a slower onset of action, although it can be useful in sustaining control of pain with sustained-release medications for a long time. The advantage of this form of medication delivery from the buccal route is its initial effect and avoidance of "first-pass hepatic metabolism." Whereas oral and mucosal forms offer important advantages in pediatric patients over other forms, which are more generally used, three significant areas remain problematic: biological aspects, governing aspects, and formulation design aspects, as illustrated in Figure 1.

According to the "International Council for Harmonization ICH topic E11 (CPMP/ICH/2711/99) and ICH E11 (R1)", this group can be further subdivided into: "Preterm newborn infants-from birth to the expected date of birth plus 27 days as depicted in Figure 2; Term and Post-term newborn infants-0–27 days; Infants and Toddlers-from 28 days to 23 months; Children-2–11 years; and Adolescents-from 12 years to 16–18 years," depending on the country.[7]

BIOLOGICAL ASPECTS

Pediatric patients are generally considered to range from birth to either 16–18 years of age, depending on the classification as shown in Table 1.[8] The division of children into different treatment groups based on chronological age is somewhat subjective, in that it largely ignores other key pharmacokinetic parameters, including "renal and hepatic function, volume of distribution, lipid solubility, and blood volumes relative to one another." This can be problematic, especially since certain formulations are designed to be age-specific or require dosing based on body weight. Consequently, the acceptability and suitability of different dosage forms across various pediatric age categories need to be thoughtfully evaluated.

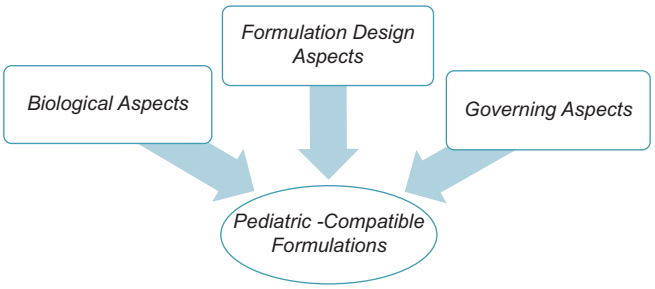

Figure 1: Challenges associated with pediatric compatible formulations

Table 1: Pediatric age classification system

Classification	Age category
Newborn	0–27 days
Newborns to toddlers	28 days to almost 2 years
Minors	2–11 years of age
Young adult	12–18 years of age

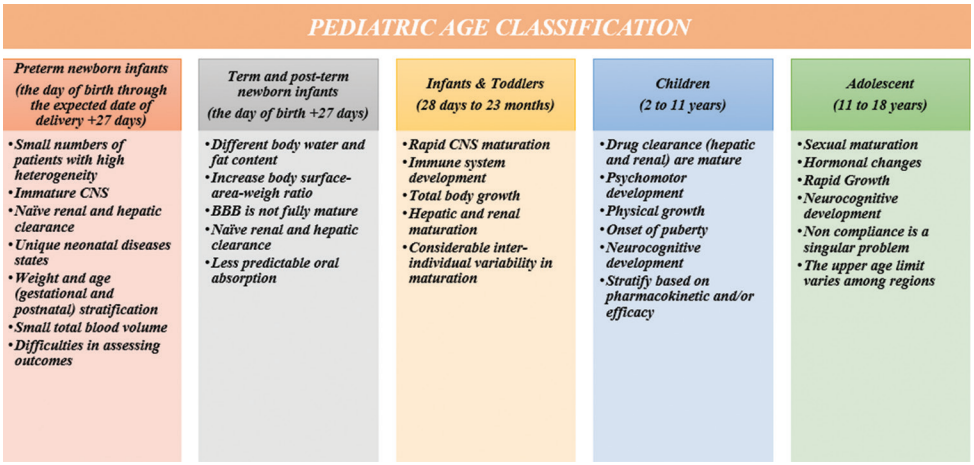

Figure 2: Overview of the International Council for Harmonization guideline E11(R1), which classifies pediatric patients according to their age

Several clinical and biological factors must be considered during the formulation of buccal dosage forms for pediatric patients:

Variability in pediatric patient profiles

Variability in children, ranging from 0 to 17 years of age, enormously challenges the development of pediatric compatible formulations suitable for this age category due to differences in preferred taste, drug-related adverse effects, and diseases that will impact the doses and dosage forms needed.[8] Moreover, the pediatric population may respond differently to therapeutic agents and formulation aids due to various biological changes in the body.

Adherence factors by age category

It is challenging for formulation design to ensure age-specific compliance. Compliance can be sophisticated and depends much upon caregivers, especially with the younger child or the child with changing disease states. With pediatric patients, cognitive levels may change as they grow, which influences ability to adhere to prescribed formulations. The caregivers are important in administering the drug.[9] Therefore, it is essential to choose age-specific formulations to improve flavor choices and meet specific needs.

Saliva secretion dynamics

To perform the absorption of drugs with oral and mucosal formulations, the existence of saliva is required since the aqueous environment this conducts really accelerates drug release, dissolution, and further absorption. The flow rate, as well as the composition, of saliva changes over time in a human lifetime. This flow rate normally increases up to about 5–6 years of age and then decreases, while the average content of electrolytes increases with age. Moreover, the salivary flow rate in the buccal mucosa of children is markedly lower as compared to adults, that is, (0.22–0.82 mL/min versus 0.33–1.42 mL/min).[10,11] The degree of hydration provided by saliva is directly correlated with the difficulty of swallowing objectionable drugs. In contrast, patients with a high saliva flow rate may experience premature medication swallowing due to the "saliva washout effect." This can lead to uneven medication dispersion in the saliva and reduced absorption of the drug through the mucosal tissues, leading to inconsistent overall bioavailability.

pH influence on drug absorption in the gastrointestinal tract (GIT)

The pH of the GIT varies both on a tissue-to-tissue basis and also with the patient's age. These differences have significant effects on the solubility and diffusion of drug formulations, and Favor unionized forms. Diseases, drugs given in treatment, nutrient intake, and saliva flow rate are factors influencing the pH of the oral mucosa. In general, pH tends to increase in proportion to the increase in the saliva flow rate. Newborns have an intragastric pH of over 4, and the activity of intestinal cytochrome P450 increases as they grow older. Oral mucosa pH averages at about 6.78 ± 0.04 in healthy adults and 6.64 ± 0.44 in pediatric patients.[12,13] A great variation is noticed among drugs in their pharmacology and among dosage forms for adults compared with children. Such variability arises from the fact that pediatric patients differ in absorption, distribution, metabolism, and excretion profiles, particularly during childhood within the 1st few years of life.[14]

FORMULATION DESIGN ASPECTS

Pediatric s represents a population with their unique needs for pediatric-compatible formulations and dosage forms, conditions that represent challenges different from others associated with different patient populations. One major challenge in developing pediatric dosage forms is finding a suitable formulation in relation to the age of the patient. These include the "dosing regimen; that is, dose accuracy, flexibility and frequency; route

of administration; dosage form; compatibility and stability of ingredients; suitability and regulatory compliance of excipients; and patient adherence." The subsequent is important especially because, in most pediatric patients, non-adherence arises due to problems in the ingestibility and flavor acceptability of oral and mucosal formulations.[15]

Tablet and capsule dosage forms are generally inappropriate for the pediatric population <4 years old, and most available for use in older children are not the correct strength. Whereas tablet fracturing is very common, it tends to yield a therapeutic or variable dosing.[16] The most common oral liquid dosage forms used for pediatric patients are solutions and suspensions. Other commonly used buccal dosage forms include lozenges, gummies, chewing gums, and lollipops, as illustrated in Figure 3. Different oral and buccal dosage forms. Liquid extemporaneous preparations are generally considered an alternative where commercial liquid preparations are not commercially available. However, compounding of pediatric formulations, especially in newborns, is complex and challenging for healthcare providers. An even more problematic area encompasses inadequate dosing of many drugs, particularly when it comes to treating critically ill neonates. In a U.S. hospital setting, oral medications for children are often prepared in largely idiosyncratic ways: "Formulas" are employed, though these are not standardized, and little is known about stability.

If commercially available pediatric formulations are not available, granular powders and sometimes, capsules may be used as a provider for compounding a formulation drug. However, one should understand how to elucidate formulation components to guarantee the production of a reliable and beneficial children's formulation. For instance, lorazepam bulk powder can be an important source of drug preparation of oral suspension for pediatric patients; however, commercial lorazepam injection cannot be used because it contains a high amount of "propylene glycol." Such excipients as "propylene glycol" may become very toxic to neonates when its dosage is quite high.[17,18]

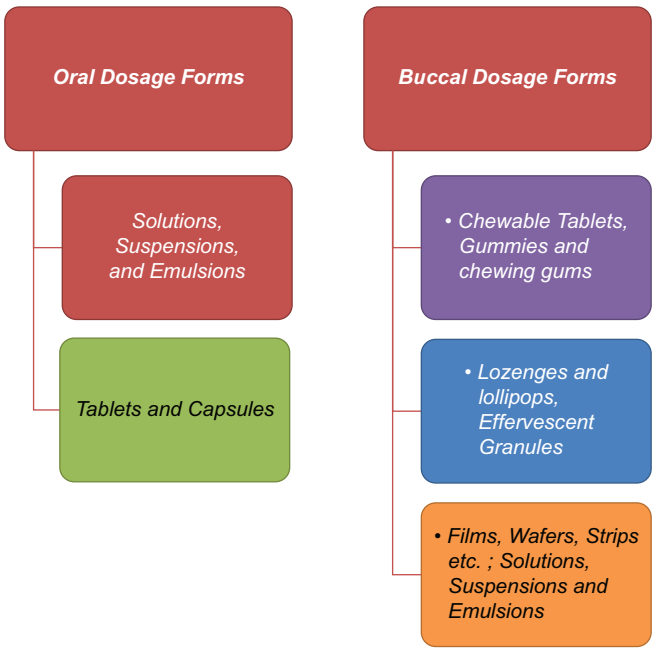

Figure 3: Pharmaceutical formulations for oral and buccal use

Additives and excipients may also be included in tablet formulations and increase the viscosity of an oral solution or suspension. Concentration may need to be adjusted if a particular rheology is desired.

SELECTION OF DOSAGE FORMS

After the dosage determination, suitability for the desired age group, so that it may be given without posing problems in respect of acceptability or swallowing, is an important consideration in the development of oral pediatric pharmaceuticals. Probably the most important factor affecting patient compliance is taste, since the bitter or metallic Flavors of unmasked formulations may not be acceptable to children, and masked formulations may also be rejected by them. Another reason for dosage rejection by children is that they may not like large volume dosages. The characteristics of a formulation's taste include "flavor, sweetener use, pH, color, and mouthfeel." Other crucial variables for designing pediatric formulations include "dosage, stability, preservation, packaging, and the required administration devices or techniques." For example, the physical and chemical properties of the drug molecule have to be known to evaluate if it would be absorbed via the buccal route when examining buccal dosage forms. More bioavailability of the drug would be achieved if the solubility is more than 1 mg/mL, having a molecular size of <500 Da, along with falling within 10–1000 log P lipophilicity and remaining unionized at the buccal pH levels.[19,20] Thus, pika of a drug is a very significant parameter since it defines the ionization at varied pH values, which in turn affect the solubility, absorption, and hence the bioavailability of the drug.[21]

Oral liquid preparations such as solutions and suspensions are generally an excellent oral form for the pediatric population since it can easily be swallowed by them. Formulations are made by dissolving or suspending the drug in suitable water-soluble diluents.[22] Liquids dosage forms for buccal delivery are difficult for pediatric patients because they tend to be poorly retained in the oral cavity and swallowed prematurely before absorption through the mucosa can take place, leading to a significant flow of medication in uncontrolled disposition across the oral region. Hence, there is a demand for research into pediatric-compatible dosage forms, including the safety of pharmaceutical technologies, such as mucoadhesive substances, that could address the issue of short contact time. The solubility of a drug can restrict both the dosage and the volume of liquid formulations administered.

To overcome this problem, cosolvents or surfactant agents might be needed in the formulation. Sweeteners and flavors

may be used to cover unpalatable tastes. If this does not work, then more complicated formulation techniques must be adopted. These include encapsulation of the drug particle.[23] However, consideration of these approaches in pediatric patients must be something put into consideration, as they may respond to excipients differently than adults. Compared to buccal tablets or conventional effervescent tablets, effervescent buccal disks are thinner and flatter, hence may lead to faster release of the drug and more rapid onset of action. When exposed to saliva, these disks liberate carbon dioxide, which acts as a permeability modifier. This formulation is an appealing drug delivery system for children use due to its improved bioavailability, but additional research is required to assess the safety of the ingredients of the formulation used in this dosage form preparation.

Lozenges and Lollipops: The formulations that are in the solid form release in the mouth by way of dissolution or disintegration of drugs in a taste-enhanced and sweetened preparation, usually containing one or more drugs.

Patients are supposed to place the formulation between the cheek and the gum or dissolve it in their mouth to facilitate the release and uptake of drugs. This formulation offers several benefits for pediatric patients, such as easy administration, the possibility of formulation and individual customization, and prolonged contact of the drug with the oral cavity. However, the rate and severity of sucking required for dissolution and breakdown can lead to more episodes of involuntary swallowing, which may result in unpredictable absorption rates due to alterations in the pharmacokinetics of drugs.[24]

"Films, wafers, and strips" are also used in buccal administrative systems, where the drug is directly applied to the buccal mucosa. These dosage forms have obtained immense demand in the pharma world since they are all ready to use and can be easily self-administered. However, their small size has proved to be a major drawback in terms of the highest quantity of the drug that could be included. The following are some examples of buccal dosage forms and their formulating excipients as illustrated in Table 2. There is a growing trend toward pediatric-compatible formulations for a wide range of drugs.

SELECTING SUITABLE EXCIPIENTS

As such, since what may be safe to adult patients may not be safe to pediatric patients, safety concerns are important for every excipient used in pediatric formulations. Therefore, ensuring safety will be essential when selecting any excipient for pediatric formulations. The collaboration of experts in pharmaceuticals in designing an effective formulation of ingredients, identifying the least number of or types and their concentrations of required excipients, and an optimal route of administration are crucial aspects of consideration in this area of knowledge.[24] Really valuable at the start of pediatric formulation development are resources such as the "STEP (Safety and Toxicity of Excipients for Pediatrics) database." For excipients' safety profiles, one would need to consider first the daily exposure and then for how long a treatment course would last in that age range for pediatric patients.

Preserving agents

Preservatives are only required for aqueous multi-dose products, but almost totally unnecessary for solid dosage preparations. In pediatric formulations, the minimum concentration of preservatives which yet ensures adequate antimicrobial protection must be used. Although preservatives are necessary in certain medicinal products, they can cause significant side effects in the pediatric population, such as full-blown reactions ranging from "gasping baby syndrome" to more serious side effects. Any type of preservative and potential side effect should be noted with caution. Whenever possible, use medication free of preservatives, especially benzyl alcohol in infants.[25]

Strategies for taste-masking

The taste receptors are diffused all over the papillae of the tongue and mouth. After the substance has dissolved in saliva, it reacts with these receptors, and children, endowed with very well-developed sensory organs, can perceive this reaction very well. To conceal the unpleasant flavor of the "active pharmaceutical ingredients," there may be the use of flavoring or sweetening agents. The preference of a child for specific tastes would largely depend on his experiences

Table 2: Examples of buccal dosage forms and their formulating excipients

Dosage form	Active ingredient	Indication	Example of excipients in the formulation	Age of approval
Chewable tablet	Diphenhydramine Hydrochloride Benadryl®	Antihistamine	Dextrose excipient, Microcrystalline cellulose, Ethyl cellulose, Magnesium stearate	Over 6 years of age
Sublingual tablet	Buprenorphine Hydrochloride Subutex®	Pain relief	Lactose monohydrate, D-Mannitol, Magnesium stearate powder, Sodium citrate powder, Deionized water and ethyl alcohol	Over 6 years of age
Buccal solution	Midazolam Hydrochloride Versed®	Antiepileptic	Sodium chloride solution, Sterile water for injections, Muriatic acid, and sodium lye	Over 3 months of age

and cultural background. Such preferences must therefore be addressed as the pediatric dosage forms are developed to ensure acceptability and compliance.[26] Although innovative pharmaceutical technologies have been extensively developed to mask the taste of drugs, it is vital to assess the safety of these technologies, as depicted in Figure 4, along with their ingredients and solvents, in pediatric patients.

Sweetening agents

The sucrose is very commonly used in pharmaceutical formulations as a sweetening agent because it is easily hydrolyzed within the intestine. However, the mucosa-bound enzymes can release significant quantities of fructose and glucose, which are then absorbed from the lumen.[27] In pediatric patients, sucrose should always be replaced by a sucrose-free alternative such as aspartame, glycerol, or any other, because sucrose causes dental caries and leaves marks on children's teeth. Sucrose, therefore, is a constituent that should also be strictly avoided in pediatric diabetic patients and those who suffer from fructose intolerance as well. Hill *et al*. On the other hand, it has even been revealed that out of the 160 oral liquid and chewable pediatric medicines studied, sucrose concentrations in certain preparations as high as 80% while there were only four antibiotics that remained sucrose-free.[28]

"Aspartame" is a synthetic sweetener that has a sweet potency 150–200 times greater than that of sucrose. As a peptide made up of two amino acids, "aspartic acid and phenylalanine," that constitutes a hazard to pediatric patients with phenylketonuria.[29] Furthermore, intake of aspartame in excessive amounts may be neurotoxic and can induce seizures. Due to these reasons, aspartame needs to be labelled at the

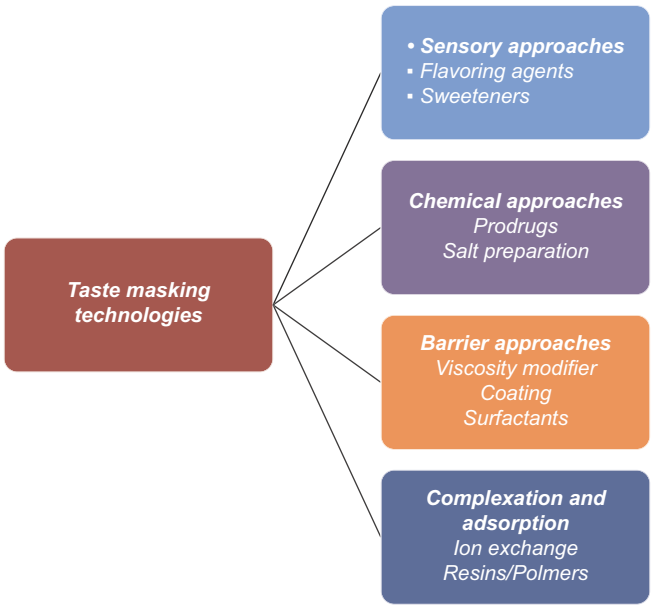

Figure 4: Evaluating pediatric safety of taste masking technologies

acceptable amount used in the formulations. Alternatives for aspartame in pediatric formulations are "Stevia, date sugar, maple sugar, maple syrup, molasses, and agave nectar."

In newborns, the build-up of sorbitol causes diabetic complications, including retinopathy and cataracts, so its content in pediatric preparations is generally limited to 0.3 g/kg.

Coloring agents

Pediatric patients prefer colored preparations due to which identification and acceptance can be enhanced; agents used for coloring, however, must be avoided except when necessary.[29] Many regulatory agencies across the globe do not permit the use of coloring agents like tartrazine, for instance, due to reported associations with hypersensitivity reactions and attention deficit hyperactivity disorder in children.[30] Exemptions for pediatric formulations: Coloring agents like azo dyes are to be avoided. Exogenous coloring agents derived from natural origin cause much ado since even after extraction, the traces of proteins are left behind, which may provoke allergies.[31] Instead, vegetable dyes like annatto and malt beta-carotene and sometimes even their omission is permitted.

Mucosal adhesive substances

Mucoadhesive substances utilized in oral and mucosal formulations enhance the duration of contact and the rate of drug delivery at the site of absorption. Poly(acrylic) acid derivatives are the most commonly used mucoadhesives in formulations, functioning by forming hydrogen bonds with mucin.[32] Another mucosal-binding polymer, polyvinylpyrrolidone, offers the benefit of stability across a wide range of pH levels. However, safety evaluations are crucial for thoroughly assessing the application of these novel pharmaceutical technologies and substances in pediatric individuals.

Permeation-enhancing agents

Otherwise known as a "penetration or absorption enhancers," permeation enhancers "increase the rate of absorption of drugs into biological membranes through the enhancement of drug partitioning in the oral epithelium and prolongation drug retention on the surface of the buccal mucosa."[33-35] The best-known permeation enhancers are "surfactants and bile salts," although their safety profiles must still be determined for pediatric use.

SAFETY CONSIDERATIONS FOR EXCIPIENTS

The first requirement for pharmaceutical compounds and their excipients is safety. Excipients may be categorized

according to their likely safety profiles as potentially safe, such as water, hydrochloric acid, and starch; potentially harmful or known harmful; those with no data on safety available, such as sodium Carmel lose; and those providing only general descriptions, such as flavorings, colorants.[36]

Children often receive medications without adequate pediatric data, primarily because studies in pediatrics are scarce and even less attention has been given to excipients safety. While some may appear to be intrinsically non-toxic, several are known to be toxic; and for many, their safety is unknown, particularly as regards specific age groups. Because the oral intake of some excipients leads to higher than intended circulating concentrations owing to distinctions in their "absorption, distribution, metabolism, and excretion (ADME)," adverse effects associated with their unobserved effects that could not be seen in other age groups may occur in children.[37]

Excipients have been associated with specific toxicity issues, such as hypersensitivity/allergic reactions, intolerance, interference with absorption of the active moiety, and interactions with that active moiety. Ethanol, for example, is commonly used as a solvent and preservative in pediatric liquid preparations, such as certain iron and furosemide products, and is also commonly found in over-the-counter preparations.[38] Newborns, infants, and children metabolize ethanol less efficiently than adults; therefore, they are more susceptible to acute and chronic toxicities associated with alcohol.[39]

Benzyl alcohol, which is also used as a preservative in many parenteral medications, is metabolized in the body to benzoic acid. This is then conjugated to form an excretable compound. However, less active conjugation of benzoic acid, and consequently the potential for accumulation, occurs in the immature metabolism present in preterm neonates and in children up to 3 years of age.[40]

The toxicological risks of a number of excipients are particularly great for children, especially neonates. Pediatric formulations require sweeteners and flavoring agents to enhance palatability, but should otherwise limit or avoid carbohydrates, which may increase glucose levels, such as "fructose, glucose, or sucrose," in diabetic children. Many of the allergic reactions are also associated with flavoring agents, which are further complicated by little information on what, exactly, is in these complex mixtures.[41]

CONCLUSION

The formulation of pediatric dosages poses multifaceted challenges that are fundamentally distinct from those encountered in adult pharmaceuticals. These complexities stem from variations in taste preferences, self-administration capabilities, and drug-related toxicities. Pediatric patients often demonstrate heterogeneous responses to medications, attributable to physiological differences in membrane permeability, enzymatic activity, pharmacokinetics, and pharmacodynamics. Nevertheless, the oral route remains the most pragmatic approach for administering medications to children, with buccal formulations emerging as a particularly attractive and accessible alternative. Formulation scientists must exercise meticulous discernment in selecting dosage forms and excipients to accommodate the unique needs of pediatric patients, all while minimizing the risk of adverse reactions associated with inactive ingredients. Fortunately, these excipients are generally well tolerated across the pediatric population. The increasing availability of comprehensive labeling information, coupled with heightened scrutiny regarding the use of such products, equips healthcare professionals to make judicious choices regarding child-friendly formulations. Legislative frameworks, such as the BPCA and the PREA, have significantly bolstered pediatric research; however, further concerted efforts are imperative to develop formulations specifically tailored for children, particularly for medications that were introduced before these legislative initiatives. This endeavor may necessitate regulatory amendments designed to incentivize the adaptation of existing pharmaceuticals for pediatric use. Given the unique and often underdeveloped physiological characteristics of the pediatric population, careful consideration is essential when prescribing medications. Therefore, the establishment of robust pediatric drug regulations in India, akin to those in more developed markets, is crucial to safeguarding the health and well-being of the nation's children. In conclusion, a concerted effort is required to enhance pediatric drug development and improve health outcomes for pediatric patients through the implementation of comprehensive and effective regulatory guidelines.

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