ADVANCED FORMULATIONS OF PEDIATRIC MEDICINES: REDUCTION OF SYNTHETIC EXCIPIENTS AND THEIR IMPORTANCE FOR CHILDREN'S SAFETY

Merita DAUTI[1]*, Sihana A. LIKA[1], Gjylai ALIJA[1], Lulzime BALLAZHI[1], Edita A. IDRIZI[1], Arlinda H. ZAJMI[1], Drita Y. HAVZIU, Flora DOKO[1], Qahil IRAIMI[1], Arianita MUSA

[1]Department of Pharmacy, Faculty of Medical Sciences, University of Tetova, Tetovo, Republic of North Macedonia
**Corresponding Author: merita.dauti@unite.edu.mk*

Abstract

Development of pediatric medicines can be considered one of the most complicated and challenging spheres of pharmaceutical science, which is due to specific physiological, biochemical, and developmental properties of the children's body. Traditionally, medicinal products designed for use by children contain various synthetic excipients including sucrose, sorbitol, sodium benzoate, parabens, ethyl alcohol, and artificial dyes aimed at improving palatability, stability, and visual appearance of the preparation. Contemporary studies suggest, however, that such excipients can pose some threats to children's health including allergy, metabolic disturbances, neurotoxicity, hepatotoxicity, as well as potential impact on pediatric development in the long run.
The purpose of this study is to critically analyze synthetic excipients used in pediatric pharmaceutical preparations and highlight safety concerns associated with their presence. At the same time, alternative approaches in the field of pediatric medicines, including using of natural alternatives and novel pharmaceutical technology solutions that would allow eliminating the use of synthetic excipients will also be explored. The methodology involves conducting a literature review and analyzing international documents on the subject matter.

Keywords: pediatric medicines, synthetic excipients, safety, natural alternatives, pharmaceutical formulations

Introduction

Pharmaceutical formulations designed for children are characterized by high specificity and complexity, which makes them different from formulations used by adults. Such distinction lies in specific physiological, biochemical, and developmental properties inherent to children. It is important to recognize that children cannot be treated as "small adults" because their bodies continuously grow and develop, influencing significantly on pharmacokinetics and pharmacodynamics of drugs and posing a special risk for neonates and infants, whose hepatic and renal systems function improperly yet.
Pharmacokinetic and pharmacodynamic parameters of medicines in children vary depending on age, weight, sex, as well as general state of health. This calls for precision and individualization of dose prescription to avoid possible overdose or insufficient amount of medicine prescribed.
Another important factor in the pharmacotherapy of children is the acceptability of medicines among them. Such attributes of medicines as their taste, smell, dosage form, and route of administration play a significant role in determining patient compliance. Refusal from drugs often occurs in children and may lead to the lack of efficacy. Therefore, children require the application of specially developed medicines rather than adapted versions of those used by adults. Application of off-label drugs and alteration of dosage forms may increase the risk of medication errors in pediatric practice.
Excipients play an important role in pharmaceutical formulations. Their functions include improving physicochemical properties, stability, appearance, and general acceptability of

medicines. The significance of excipients increases when developing pediatric medicines since their presence improves taste, smell, and appearance of the medicine, which affects patient compliance positively.

The choice of excipients takes place at the pre-formulation stage of preparation of a medicinal product. In case of pediatric medications, a detailed analysis of all safety factors should be made since there are many synthetic excipients that demonstrate some adverse effects on children. They include allergies, digestive disorders, and even neurologic problems in children, especially neonates and infants whose metabolic system is not developed completely. Moreover, certain excipients are likely to accumulate in the organism because of slow elimination.

In pediatric pharmacy, there is a lack of information about the long-term effects of excipients on children. Since most excipients are proven to be safe in adults, pediatric formulations contain them without conducting special studies on their impact on children. This situation stimulates the revision of existing formulations and search for safer analogs of medicines. It means that replacing and minimizing usage of certain synthetic excipients with other compounds may be beneficial in this situation. The purpose of such an approach is reducing risks for children.

This paper aims at contributing to the scientific literature through discussing advanced pediatric formulations and the benefits of lowering the content of synthetic excipients for child safety.

Objective

The objective of this paper is the analysis of scientific information related to the issues of pediatric formulations with special emphasis on the role and impact of synthetic excipients.

Another purpose of this paper is to consider natural alternatives and new technologies that may contribute to decreasing the amount of synthetic excipients used in pediatric drugs while taking into account the issues of safety and efficacy of medicinal products prescribed for children.

Materials and Methods

Study design

This paper represents a systematic review of scientific literature dedicated to analyzing the safety problems related to the usage of synthetic excipients in pediatric formulations and assessing the prospects for using more sophisticated alternatives that could reduce or completely exclude such risks. Given the specificity of this topic, the analytical and comparative approaches were used, relying on existing toxicological and clinical studies as well as relevant regulatory documents.

Data sources and Selection criteria

Literature searches for this study involved foreign databases and official documents. Information sources used in this paper are listed in the following table:

Table 1. Information sources and Selection criteria

TYPE OF SOURCE	EXAMPLES/DATABASES	NUMBER OF SOURCES USED	SELECTION CRITERIA
Peer-reviewed scientific articles	PubMed, Scopus, ScienceDirect	45	Publications from 2005–2025 focusing on pediatrics or effects in children
Regulatory documents	EMA, FDA, WHO	10	Guidelines on the use of excipients in pediatric medicines
Reports from international organizations	EFSA, FAO	5	Evidence summaries and safety assessments of excipients
Classical/reference literature	Libraries and frequently cited articles	3	Fundamental studies in excipient toxicology

Keywords such as "pediatric formulations," "synthetic excipients," "excipient toxicity in children," "parabens," "benzyl alcohol," "regulatory guidelines," and "advanced drug delivery systems" were used together with Boolean operators, including AND and OR to conduct research. All those studies focused on adult subjects, were of a non-scientific nature, or lacked a proper methodology were not considered. This approach allowed ensuring the validity and reliability of chosen information sources.

Results and Discussion

Function and Possible Harmfulness of Synthetic Excipients

Excipients are viewed as a crucial component in drug formulations performing technological functions essential for the stability, dosing, administration, and acceptability of medications. At the same time, excipients' function becomes especially important when creating pharmaceuticals intended for consumption by children characterized by limited ability to swallow, high metabolic sensitivity, and special sensory requirements. The usage of synthetic excipients has become a cause for significant safety concerns in pediatric medicines. The issue is closely linked to the physiology and metabolic immaturity of pediatric subjects (Barker et al., 2018; EMA, 2019).

Potential Toxicity of Synthetics Excipients in Pediatric Medicine

One of the major concerns about synthetic excipients in pediatric drugs involves their toxicity caused by such factors as the duration of usage and the child's physiological condition (metabolic immaturity). Neonates and infants may have limited abilities to metabolize and excrete certain excipients increasing their chances to be accumulated in the body (van den Anker et al., 2018; Yochana & Allegaert, 2020).

Propylene glycol and ethanol are two major synthetics considered concerning. According to clinical studies, prolonged exposure to the two substances can lead to the development of metabolic acidosis, central nervous system depression, and renal impairment in neonates (Valeur et al., 2018; FDA, 2018). This is why regulatory authorities stress the importance of imposing serious restrictions on the usage of the specified excipients in pediatric medicine.

Allergic Reactions and Intolerance Effects

It is possible to speak of the development of allergic reactions and intolerances in the context of pediatric medicine. It has been found that artificial colorants and preservatives can cause skin reactions, urticaria, and digestive issues among children (Lass et al., 2019). Such effects can adversely impact therapy and patient outcomes.

Cumulative Effect of Synthetic Excipients in Pediatric Treatment

Another crucial, but frequently overlooked, element concerning the application of synthetic excipients in pediatric medicine is the effect of cumulative exposure. Due to the frequent administration of more than one pharmaceutical product in children suffering from chronic conditions, these patients might be subjected to multiple simultaneous exposures to synthetic excipients coming from different drug formulations (Lass et al., 2019; Valeur et al., 2018).

While the intake of active substances is carefully regulated and controlled, excipients do not always become an integral part of the therapeutic process. Thus, their dosage can exceed the safe boundaries, especially when dealing with excipients like propylene glycol, ethanol, and parabens that may be used in various products for pediatric use (EMA, 2019; FDA, 2018).

Observational research revealed that neonatal patients admitted to hospitals experience high levels of synthetic excipient exposure, including a prolonged period of exposure to these compounds in neonatal intensive care units.

Artificial Excipients and Their Potential Effects on Neurodevelopment

The maturation of the central nervous system during childhood is considered a crucial period where the body becomes particularly susceptible to toxins. Some artificial excipients have also been linked to adverse effects on neurodevelopment, but only in cases of their early exposure to an individual (Barker et al., 2018; van den Anker et al., 2018).

Artificial solvents like ethanol and propylene glycol are some of the most researched materials in this aspect. Because of the incomplete development of the blood-brain barrier in infants, there is a higher chance of their penetration into the central nervous system and causing neuro-depressive and neuro-toxic effects (FDA, 2018). While acute risks are relatively well-researched, a number of questions about long-term neurodevelopmental impacts require further investigation.

At the same time, there is some experimental evidence that demonstrates the potential effects of early exposure to particular artificial colorants and preservatives on behavior and cognitive development in infants. However, this research lacks clinical data that would warrant additional research aimed at investigating these hypotheses (Barker et al., 2018; EMA, 2019).

Table. 2 Synthetic excipients frequently used in pediatric preparations and their potential risks

SYNTHETIC EXCIPIENT	TECHNOLOGICAL FUNCTION	POTENTIAL RISKS IN CHILDREN	MOST SENSITIVE AGE GROUP
Benzyl alcohol	*Preservative*	*"Gasping syndrome", neurotoxicity*	*Neonates*
Propylene glycol	*Solvent*	*Metabolic acidosis, CNS depression*	*Infants*

Polysorbate 80	*Emulsifier*	*Hypersensitivity reactions*	*Neonates*
Sodium benzoate	*Preservative*	*Hyperbilirubinemia*	*Neonates*
Artificial colorants	*Colorants*	*Allergic reactions, hyperactivity*	*Young children*

Sources: Turner et al. (2014); Nellis et al. (2020); EMA (2019).

Regulatory Approach to the Utilization of Synthetic Excipients in Pediatrics

The issues related to the utilization of synthetic excipients in pediatric formulations have been known for a while, prompting international regulatory organizations to issue specific guidelines concerning this topic. Thus, such organizations as EMA, FDA, and WHO have issued recommendations in an effort to enhance the clarity and safety of using synthetic excipients (WHO, 2010; EMA, 2019; FDA, 2020).

Among the main requirements formulated by these agencies is the disclosure of all ingredients used in a product, alongside an evaluation of the safety profile of these synthetic ingredients in a pediatric population. For instance, EMA noted that, when used in pediatrics, certain synthetic excipients that could trigger side effects should come with a warning (EMA, 2019). However, although this regulation exists, there remain numerous gaps in understanding the clinical and toxicological aspects of many synthetic excipients. This circumstance motivated the creation of such programs as Eu PFI (Salunke et al., 2016).

Toxic or Problematic Excipients in Pediatrics

Benzyl Alcohol – Toxicity and Impact on Pediatrics

Benzyl alcohol is an excipient used in the pharmaceutical industry as a preservative and solvent in various formulations. Despite the generally acceptable safety of benzyl alcohol in adults, in recent decades, it has been proven that the use of this excipient carries a significant toxic risk in newborns and small children due to their special physiological features (EMA, 2019). Patients of this age have metabolic immaturity that increases their sensitivity to toxic compounds formed during the metabolism of this excipient. The incomplete development of the enzymatic system responsible for conjugation results in the accumulation of benzoic acid in blood plasma that may lead to various toxic reactions ranging from metabolic acidosis and brain dysfunction to organ failure and even death (Young & Jewell, 2000; EMA, 2019).

Regulatory requirements concerning the safety of benzyl alcohol in the pediatric population are regulated by EMA and ICH guidelines. Specifically, according to EMA (2019), medicines with benzyl alcohol as an excipient should have a warning label in product information leaflets concerning the risks related to neonatal use. For preterm babies, whose metabolic systems are not well developed, this additive should always be avoided and resorted to only if there are no other safer options.

Sodium Benzoate

Sodium benzoate is an excipient which is commonly used in pharmaceutical manufacturing and is primarily applied as a preservative in various oral liquids, syrups, and solutions. Nevertheless, although this chemical is beneficial from a technological point of view, sodium benzoate poses significant risks for children and newborns since they have not yet fully developed their metabolic systems. In other words, the immaturity of the hepatic conjugation system in young infants, especially in premature babies, can cause the build-up of benzoic acid in blood plasma, which will likely cause metabolic acidosis (EMA, 2019). Metabolic acidosis in newborns is a critical condition which can involve central nervous system suppression, respiratory issues, and hemodynamic imbalance.

Concerning regulatory issues, the European Medicines Agency provides that it is crucial to include the information about sodium benzoate in the labeling of the medication and provide warnings when using the drug in neonates (EMA, 2019). As per modern recommendations for pharmaceutical development as stated by ICH Q8 guidelines, the choice of excipients should always be made taking into account both their benefits and risks, as well as physiological maturation of the child (ICH, 2009).

Sorbitol

Sorbitol is a sugar alcohol or polyol that is commonly employed in the production of drugs as a sweetener, humectant, and flavor enhancer in oral pediatric formulations like syrups, solutions, and suspensions. Owing to its sweetness and lower glycemic index compared to sucrose, sorbitol can be considered an ideal choice for formulations for children in situations where there is a need for avoiding fermentable sugars (Rowe, Sheskey & Quinn, 2009). Nonetheless, in spite of its frequent use and relative safety as an excipient, sorbitol poses a number of clinical risks when used by children, especially if administered in high doses or repeatedly.

Pharmacokinetically, sorbitol is poorly absorbed in the intestines, and it is mainly absorbed passively. A large amount of the compound is not absorbed and moves to the colon, where it is metabolized by the bacteria in the gut to short chain fatty acids and gases (Livesey, 2003). The aforementioned mechanism is responsible for the laxative effect of sorbitol. It acts in the intestinal lumen by raising osmotic pressure through the attraction of fluid in the gut causing diarrhea, abdominal pain, and distension.

Yet another critical factor is associated with the potential pharmacokinetic interaction of sorbitol with some pharmaceuticals. Specifically, sorbitol may alter the absorption rate of some drugs due to its influence on gastrointestinal motility and shortened mucosal drug contact time (Chen et al., 2007). The latter issue is especially relevant in pediatrics since drug bioavailability is essential for attaining a satisfactory therapeutic outcome.

European regulatory bodies consider that information concerning sorbitol content should be provided in the label and patient information leaflets, provided that its presence in oral medicines surpasses the threshold that might induce the onset of a laxative effect (EMA, 2014). In addition, medical personnel is supposed to evaluate the total intake throughout the day, especially in case of several polyol-containing formulations administered to the child.

Sucrose

One of the most widely used excipients is sucrose, also known as table sugar. This substance can be used for improving the taste and facilitating the administration of drugs by children since sucrose improves the taste of medicines (EMA, 2019). It can also be used in pediatric oral liquids, syrups, and preparations that cause some difficulties during swallowing. In addition, sucrose can serve as a stabilizer and a sweetener that masks the unpleasant taste of many active ingredients (Allen et al., 2017).

However, sucrose is considered a dangerous component for pediatric medicines because it can have an adverse impact on neonates and premature infants. In fact, the introduction of high doses of sucrose, whether intravenously or orally, might lead to the change in blood glucose levels and osmolarity (Kearns et al., 2003). Children, especially those in their first months of life, have no ability to process sugar effectively, causing hyperglycemia and even osmotic diarrhea (Hoffman et al., 2018).

Furthermore, from the toxicology perspective, sucrose causes an increase in osmotic pressure and hyperglycemia in newborns. As a result, it leads to metabolic acidosis, worsening of hydration status, and oxidative stress in newborn cells (Allen et al., 2017).

Studies in clinical practice have found instances of temporary hyperglycemia in neonatal patients who had been administered a formulation that contained a significant amount of sucrose, supporting the necessity of monitoring the blood glucose level continuously (Hoffman et al., 2018). In addition, prolonged use of sucrose in pediatric medication can have consequences on long-term health issues such as the development of cavities and insulin sensitivity in children (Allen et al., 2017).

Parabens

Parabens are synthetic chemical compounds commonly used as preservatives in pediatric medications, skin care products, lotions, and oral solutions, in order to inhibit microbial growth and increase product longevity (Soni et al., 2005). Methylparaben, ethyl paraben, propylparaben, and butylparaben are the most frequently used compounds in this group. Parabens are usually combined in order to guarantee a wide range of antimicrobial activity and chemical stability of the pharmaceutical compound (Błędzka et al., 2014). Despite being extensively employed for several decades, parabens are generally perceived as non-toxic substances in the general population; however, recent evidence indicates that the potential toxic effects of parabens on children can be significant. Children and infants have lower metabolic capabilities than adults and are therefore highly vulnerable to accumulating toxic levels of parabens (Schettler et al., 2012). The administration of paraben-containing medication during infancy can lead to the internalization of this substance through skin contact or orally.

Parabens possess toxic properties because of their endocrine-disrupting characteristics and act as agonists of estrogen receptors. Several experimental studies indicate that the chronic administration of parabens affects the sexual maturation, expression of hormone receptors, and reproduction system development (Darbre & Harvey, 2008).

International regulators such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have laid down strict guidelines concerning the percentage limit of parabens that can be incorporated in the drugs and cosmetics meant for use by pediatric patients (EMA, 2019). For instance, methylparaben and ethylparaben should never surpass

0.4% individually while propylparaben and butylparaben should not surpass 0.14% each. Combining parabens is a delicate exercise, and utmost care needs to be taken to prevent harmful effects.

Propylene Glycol

Propylene glycol, alternatively referred to as 1,2-propanediol, is a frequent ingredient used in pediatric drugs, where it acts as a solvent, stabilizer, moisturizer, and flavor enhancer (Kumar et al., 2016). The hygroscopic nature of this substance ensures that the moisture content of products is retained as well as maintaining the stability of other active ingredients in the formulation. Propylene glycol is commonly used in oral liquids, syrups, creams, and IV solutions for children and infants (EMA, 2019).

Even though the inclusion of propylene glycol in drugs is deemed to be relatively harmless in adults, young children, including neonates and preterm babies, tend to experience adverse reactions to its presence because of the low metabolic potential (Kearns et al., 2003). Propylene glycol undergoes degradation within the body, leading to the production of pyruvic acid and lactic acid. Small amounts of this substance are also excreted through urine (Sethi et al., 2017). Neonatal and premature infants have less enzymatic potential and renal activity, thus making them susceptible to adverse effects.

The reported adverse health outcomes comprise metabolic acidosis, central nervous system depression, hemolysis, and nephropathy. The clinical symptoms of propylene glycol poisoning in infants are lethargy, hypothermia, tachycardia, and hyperlactemia (Sethi et al., 2017; Kearns et al., 2003). The continuous administration of IV medications containing propylene glycol, such as antibiotics and anticonvulsants, has been associated with a few cases of toxic overload, necessitating vigilant clinical supervision.

To mitigate the risks, the governing bodies, including the European Medicines Agency, have set strict limits on the maximum percentage of propylene glycol in pediatric pharmaceuticals. For oral formulations, the maximum concentration level should be below 20%, whereas for IV formulations, the maximum allowable daily dose of propylene glycol for infants should be less than 1 g/kg (EMA, 2019). Whenever feasible, it is recommended to prescribe formulations devoid of propylene glycol or with other safer excipients, particularly premature infants and those with renal/ hepatic impairment.

Artificial Colorants

Artificial colorants are extensively used in pediatric medicines due to their ability to enhance the visual appeal of preparations and increase their acceptability by children (Wang et al., 2020). This excipient increases the acceptability and reduces refusal of medicines among children. Artificial colorants are mostly chemical analogs of azo dyes and may include such substances as tartrazine (E102), sunset yellow (E110), allura red (E129), and ponceau 4R (E124) (EMA, 2019).

Nevertheless, the application of artificial colorants in pediatric medications has led to severe issues related to the safety of patients because of their adverse impact on hyperactivity, allergies, as well as the toxicity of the nervous and metabolic systems (McCann et al., 2007; Stevens et al., 2013). Various clinical and epidemiological studies proved that colored foods and beverages had an effect on the emergence of ADHD in children. Consumption of azo dyes

was associated with increased motor activity, low concentration, and behavioral problems (Stevens et al., 2013).
From a toxicological point of view, certain synthetic colorants may induce allergic responses, such as urticaria, asthma, and allergic rhinitis, particularly among children who have an inherent tendency for allergic response (Wang et al., 2020). Toxic manifestations at the systemic level may involve alterations in hepatic enzyme activity, alterations in gut microflora, and oxidative stress seen in experimental animals (Kumar & Sharma, 2018).

Polysorbate

Polysorbates are surfactants and emulsifiers that are often employed as excipients in pediatric medicines due to their ability to increase stability in liquid medications, enhance solubility of pharmacologically active compounds, and inhibit particle sedimentation in suspensions and emulsions (Rowe et al., 2009). Nevertheless, polysorbates do present certain toxicological hazards. It has been demonstrated that surfactants may induce allergic reactions and affect cell membrane stability (Cavaliere et al., 2018). Anaphylaxis and hypersensitivity reactions following contact with Polysorbate 80 in pediatric patients have been occasionally reported, especially when it was applied in the intravenous administration of vaccines or formulations of sensitive medications (EMA, 2019).
In addition, there is evidence for the effect of polysorbates on the gastroenterological and metabolic systems. In vitro and animal trials have suggested that Polysorbate 80 may influence the composition of the intestinal microbiome and the permeability of the intestinal mucosa (Chassaing et al., 2015). This feature is especially pertinent to young children since their intestinal microbiome is still in development, and epithelial barriers are prone to disruption.
The last point to consider is the potential link between the use of Polysorbate 80 and inflammation, as well as the development of immunological properties. According to Cavaliere et al. (2018), polysorbates might induce the release of pro-inflammatory cytokines, which can impact the function of immune cells. This issue is highly important for children who are genetically predisposed to developing immune-related conditions and allergies.
Therefore, when prescribing medications containing Polysorbate 80, special care should be taken to minimize the exposure of children to this substance, substituting it with safer analogues like phospholipids or surfactants, which have been approved for use among children (EMA, 2019; FDA, 2020).

Ethanol

Ethanol is a common excipient employed in pediatric medications, primarily as a solvent for poorly soluble active ingredients and as a preservative in some liquid preparations (EMA, 2019). The ethanol content in pediatric medications normally varies between 0.1% and 10% v/v, depending on the nature of the medication, the administration route, and the age of the patient (WHO, 2017). Nonetheless, ethanol is an excipient that raises toxicological concerns among pediatrics. Due to their immature enzyme systems, infants and toddlers metabolize ethanol slower compared to adults, who possess higher levels of alcohol dehydrogenase enzymes in their liver (Farah et al., 2016). Thus, the chances of ethanol accumulation increase, potentially leading to toxic reactions such as hypoglycemia, brain impairment, metabolic acidosis, and, in severe cases, coma and even death (EMA, 2019; WHO, 2017).

Several clinical studies have demonstrated that an exposure of an infant less than 6 months old to ethanol through oral means can lead to a significant increase in blood alcohol concentration even after low-level consumption, which makes this age group highly vulnerable (Farah et al., 2016). Theoretically, from the point of view of neurotoxicity, ethanol is considered a depressant of the central nervous system, and its intake by infants can impair the development of the brain. It has been proven through the results of experimental studies and epidemiology that repeated exposure of infants to substantial doses of ethanol leads to cognitive impairment, skill acquisition difficulties, and increased likelihood of behavioral problems in childhood and adolescence (Chatterjee et al., 2018). Moreover, the effect of ethanol on glucose metabolism and glucose levels in the blood cannot be neglected. As was mentioned before, infants are highly prone to ethanol-induced hypoglycemia owing to their inability to perform gluconeogenesis properly (Farah et al., 2016). It causes tremors, lethargy, seizures, and coma, especially when ethanol is used simultaneously with drugs that affect glucose metabolism.
The pharmaceutical regulatory agencies such as EMA and FDA have clearly outlined the allowable limit of the use of ethanol in the pediatric medicines and also clearly labeled the percentage of alcohol present in the medicine according to different age groups (EMA, 2019; FDA, 2020). For instance, EMA advises that the medicines used by children below the age of six years should not contain more than 0.5% ethanol while for children above the age of six years, the limit is 5% of ethanol.

Natural and Biocompatible Alternatives in Pediatric Formulations

The advancement of safety in pediatric medications has promoted growing scientific research into natural and biocompatible excipients as alternatives to synthetic excipients. The purpose of alternative excipients is to deliver equivalent functionality to synthetic counterparts without increasing the risk of adverse reactions and enhancing tolerance in children. According to contemporary literature, natural excipients in pediatric pharmacy are considered a prospective trend, given the highly sensitive physiology of children (Salunke et al., 2016; Strickley, 2019).

Natural Polymers as Substitutes for Artificial Excipients

Among the most extensively researched classes of biocompatible substitutes in pediatric formulations are natural polymers. Compounds like cellulose and its derivatives, alginates, pectins, gelatin, and chitosan have found widespread application for diverse technological purposes, including stabilization, thickening, and modulation of the release of active ingredients (Thakkar et al., 2020). The microcrystalline form of cellulose, along with its derivatives, for instance, hydroxypropyl methylcellulose, is regarded as one of the safest excipients in pediatric formulations owing to its biological inactivity and non-systemic absorption. Alginates and pectins derived from plants have been employed as gelling and stabilizing agents in pediatric suspensions and syrups. Research demonstrates that natural polymers provide significant benefits with respect to biocompatibility and biodegradability, thereby minimizing the requirement for artificial preservatives (Nelis et al., 2021).

Natural Excipients for Enhancing Tastiness and Acceptability

The sensory acceptability of medications plays an essential role in their compliance among children. One of the main factors leading to the rejection of drugs prescribed to children is their unpleasant taste, thus promoting research into alternative natural substances for artificial sweeteners and flavorings (Gómez-Orellana, 2021). For instance, natural sweeteners like sucrose, fructose, stevia, and agave syrup may serve as safe alternatives to artificial substances like aspartame and saccharin. Despite the need for cautious usage of sucrose owing to its negative effect on dental hygiene, several studies confirm that, when administered in appropriate amounts, sucrose serves as one of the best-tolerated sweeteners among children (EMA, 2019). Moreover, natural flavoring compounds derived from fruits and fragrant plants prove to be more beneficial than synthetic substitutes due to their lower allergenicity and enhanced medicinal acceptance among children (Batchelor et al., 2018).

Vegetable Oils and Natural Lipids as Alternatives to Solvents

Natural vegetable oils and lipids have been used as alternative solvents that are biocompatible with the body, especially with children in relation to lipophilic materials. The use of oils such as sunflower oil, soybean oil, and MCT oils have proved to have a safe safety profile and acceptable metabolism (Allegaert et al., 2020). By using these natural solvents, the need for propylene glycol and ethanol is reduced due to their toxicity to neonates and infants. Regulatory agencies advise on the use of natural lipids when technically feasible (FDA, 2020).

Limitations and Challenges of Using Natural Alternatives

Despite a number of positive features, the utilization of biocompatible excipients can be associated with multiple technological difficulties as well. Some of the major problems with these compounds include chemical variation, instability, and sensitivity to different environmental factors (Thakkar et al., 2020). In addition, some natural excipients can demonstrate sensitivity to bacteria; thus, more measures are required for the preservation of the excipient’s stability and microbiological safety. This problem may be especially important for pediatric products that minimize the utilization of synthetic preservatives (Nelis et al., 2021).

Conclusion

Thus, the literature review has allowed obtaining some insights into the application of excipients in pediatrics and its impact on the health and safety of children. Firstly, it should be mentioned that most traditional medicines used for the treatment of children's diseases include synthetic excipients, which, despite being generally regarded as harmless for adults, can be potentially harmful for children, particularly neonates and toddlers. According to the results of the conducted toxicity studies, substances like parabens, sodium benzoate, sorbitol, and benzyl alcohol could lead to side effects starting with irritative effect on the stomach and ending with metabolic acidosis and grey baby syndrome caused by benzyl alcohol.

It is worth mentioning that the intensity of the exposure to excipients is determined by the physiological condition of children and their age since neonates and toddlers have lower levels of enzymatic activity and less developed hepato-renal system. Moreover, recent scientific

discoveries indicate that accumulations of certain excipients may adversely affect the efficacy of medicines since they change the processes of drugs' absorption and metabolism. Therefore, a necessity to create child-friendly formulations instead of reducing the dosages of adult medications arises.

The literature also notes that it is necessary to replace potentially hazardous excipients with safe ones or even natural substances. For instance, several studies suggest that biocompatible polymer or natural materials, including pure glucose and gelatin, can be applied successfully, thus lowering the likelihood of toxicity significantly while retaining the stability and pleasant taste of the preparation. Such a practice is especially relevant for oral preparations because sugar or other additives may trigger an allergic reaction or metabolic syndrome.

From the analysis of regulatory sources and guidelines, an international tendency towards minimizing the use of hazardous excipients has been discovered. The authors of contemporary scientific research note that children's pharmaceuticals should undergo comprehensive testing not only regarding their therapeutic impact but also concerning the safety of every auxiliary substance. The recommendations of the EMA and FDA on this issue are quite unambiguous: every excipient should be analyzed based on patients' age and weight, as well as minimizing preservatives, dyes, and artificial sweeteners.

The substitution of synthetic excipients with natural and biocompatible compounds makes medicines more acceptable and prevents any potential toxicity. The utilization of natural and biocompatible substances is a safer way of formulating medicines, particularly in vulnerable populations such as infants, and ensures greater stability, improved taste, and enhanced tolerance. Such findings support the suggestion that the pharmaceutical industry should pay attention to minimizing high-risk excipients when developing formulations.

In conclusion, the standardization of local practices to international recommendations and ongoing monitoring of pediatric medicines can be considered a good starting point for designing appropriate regulations and policies aimed at safeguarding children. Such conclusions highlight the significance of a holistic strategy where the pharmaceutical industry, healthcare professionals, and regulatory agencies assume joint responsibility for providing adequate formulations for children.

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