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Review Article

A REVIEW ON THE SOLID ORAL DOSAGE FORM FOR PEDIATRICS, REGULATORY ASPECTS, CHALLENGES INVOLVED DURING THE FORMULATION, AND TOXICITY OF THE EXCIPIENTS USED IN PEDIATRIC FORMULATION

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ABSTRACT

Designing an appropriate dosage form in medical treatment for the pediatric population is very challenging. The major challenges faced during designing the oral solid dosage form for pediatrics are also the prerequisites for the development of the dosage form, and they are, administering the drug according to the body weight and taste masking, which is followed by other factors like the safety of excipients, size of dosage form and so on. Oral solid dosage forms like mini-tablets, soluble films, and orally disintegrating tablets are a few promising dosage forms for use in the pediatric population. The obstacles, such as physiological differences between the various age groups, excipient safety, technology requirements, low profitability, clinical trial limitations, and regulatory ambiguity all have an impact on pediatric dosage form development. Recent advancement in the development of pediatrics formulations has been made due to new regulations, more financial opportunities, and novel collaborative research programs. A shift of pattern towards solid oral dosage form and an emphasis on innovative preparations, such as dispersible, flexible, as well as multi-particulate oral solid dose forms, are some of the advanceme nts. Such advancements have allowed for more flexibility of dose, easy administration, and improved medication formulation acceptance in pediatrics. In consideration of dosage forms for pediatrics, issues such as pediatric suitability, excipient selection, prospects for modified drug release formulations or fixed-dose combinations, palatability, and acceptability, as well as challenges were reviewed in the current manuscript.

Keywords: Pediatric, Solid oral dosage form, Regulatory aspects, Excipients, Toxicity, Pediatric drug delivery

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INTRODUCTION

Pediatric medicine development is receiving more attention and resources currently, intending to ensure the approval and availability of personalized and good-quality medicines for pediatrics. One of several challenges in developing age-appropriate pediatric drugs is a lack of understanding about what drugs are acceptable to children [1]. As a result, the production of the age-appropriate pediatric drug has become important, and regulatory bodies around the world have recognized the need of developing formulations for specific ages and body weights of pediatrics for different types of disorders faced by them [2]. After the adoption of the Pediatric Regulation (EC) number 1901/2006 and the emergence of expert committees in pediatrics, the focus on drug formulation and dose of the drug has increased significantly [3]. Based on their age, size, physiologic condition, and therapeutic requirements, the needs of children should be considered while developing drug formulations for pediatric pharmacotherapy. These pediatric medications are essential for administering doses safely and correctly, reducing the possibility of errors occurring during medication, enhancing medication adherence, and enhancing therapeutic outcomes in children [4]. The formulator's main attention is on delivery dosage forms, which can change if the difficulties outweigh the advantages, before evaluating the multiple challenges connected with pediatric drug delivery. For children, the oral route is the most effective mode of administration because it is invasive, painless, and needs no special training. In general, the most affordable and practical dosage forms for oral administration among the greater adult population are the solid dosage forms [5]. The oral route of drug delivery is a widely accepted route by a broad range of populations for the administration of drugs that are intended to show local or systemic absorption, despite its challenges. Oral dosage forms have a larger market share as compared to the dosage forms delivered through other routes such as pulmonary, rectal, parenteral, transdermal route, and so on. Oral dosage forms can be provided as simple liquids, dispersed systems, or solids, but they can also be fitted with patented technology to distribute the medication as intended. However, solid dosage forms are preferred over dosage forms due to the advantage of stability and convenience to carry around. From what the trend has shown, pharmaceutical companies do not consider the pediatric drug market as attractive as the market for adult dosage forms leaving it to be served by adjusting the adult dosage forms. Hence there is a requirement for a collaborative effort from researchers and manufacturers toward the development of novel drug delivery systems. With the increased number of research focused on novel systems to improve patient compliance for neonates and pediatrics, the future of drug delivery for these populations looks encouraging [6]. The advantages, types, and challenges of oral solid dosage forms, clinical studies, and patents are part of this study. The literature review was done using 'Pubmed', 'Science Direct' and 'Google Scholar as search databases by typing keywords such as 'pediatric dosage forms', 'pediatric oral solid dosage forms', and 'regulations for pediatric dosage forms' with 'review article', as filters.

Regulatory aspects

The necessity for drug authorization in the pediatric population and the numerous problems with pediatric clinical trials, among other things, served as the impetus for the development of a legal and regulatory framework for pediatric clinical research. Regulations were invented in the US in the late 1980s, and considerable advancements were made further [7-9].

United States (U. S.)

In the year 1994, Pediatric Labelling Rule was issued, which made the manufacturers perform a survey of the existing data to determine if enough information was available on drug labeling. According to the law, Manufacturers are required to submit supplementary New Drug Applications (NDAs) to the Food and Drug Administration (FDA) to request FDA approval for label changes if they decide that the information on pediatric use on the label can be modified considering current findings [10, 11]. Even though this guideline was intended to improve pediatric labeling, it only led to a tiny number of carefully planned and executed research [12].

In the year 1997, The Pediatric rule was proposed and was finalized in the year 1998. It was made to ensure that at the time of, or shortly after, approval, new medications and biological products that are expected to be frequently used in pediatrics or that offer therapeutic advantages over currently available treatments for pediatrics have satisfactory pediatric labeling for the approved indication [13]. In 2001, a report by FDA found some drawbacks in the initial legislation that was considered by BPCA (Best Pharmaceuticals for Children Act). The work done by BPCA includes regulation of public publication of the study findings, renewal of the exclusivity incentives, and establishment of a procedure for on-and off-patent medications, which involved contracts of the government for pediatric trials [12]. In 2003, Pediatric Act was enacted, which showed the requirement for the development of a plan for pediatrics that defined the assessment for pediatrics and focused on the need for the development of a dosage form according to the age of the pediatric patient [14, 15]. The acts of BPCA and PREA were reauthorized in the year 2007 under the authority of another act, the FDAAA (Food and Drug Administration Amendments Act). With the help of FDAAA, the reauthorization of BPCA extended up to the year 2012 and introduced the Paediatric review Committee, which provides a framework for obtaining information about plans for pediatrics, pediatric studies, and their assessments that aid in ensuring the consistency and quality of the dosage form [15, 16]. The FDA Reauthorization Act of 2017 includes orphan drugs for pediatric on the PREA Mandatory List, thus improving the situation for the development of pediatric dosage forms [5].

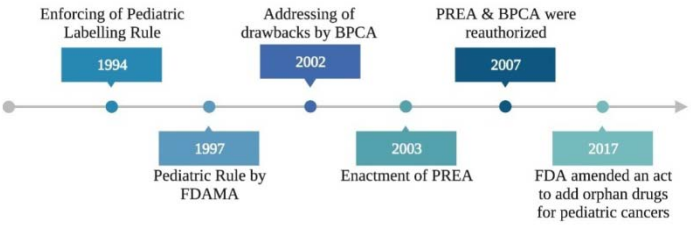

Fig. 1: Legislation in the U. S. for pediatrics [Authors creation] [5, 17]

Europe (E. U.)

The European Medicines Agency (EMA) shared the perception with The U. S., that pharmaceutical companies are legally required to do studies on the pediatric population to get information on the medications to be used for pediatrics. In 1997, a round table of experts was organized at the EMA by the European Commission to discuss pediatric medicines and to introduce a system of incentives to strengthen the legislation [18]. In the year 1998, in the context of the International Conference for Harmonization (ICH), the requirement for a global discussion on the topic of clinical trials conducted on children 1998 was supported by the commission [18]. A European guideline was established in 2001 after the harmonized tripartite E11 ICH guideline, "Clinical investigation of pharmaceutical products in the pediatric population," which was finalized in the year 2000 [16, 18]. In December 2000, the Commission was asked by the European Health Council to take special action on the issue of unapproved medications being used on children [19]. These recommendations were evaluated in the years that followed and the outcome was new legislation that governed the creation as well as approval of medications intended for pediatric use. It was implemented in the European Union (E. U.) in January 2007 after being introduced in December 2006 [20]. The European Pediatric Formulation Initiative (EuPFI) was established in 2007 to bring attention to issues relating to pediatric formulation [21]. In the year 2014, it was made mandatory to strictly follow the guidelines while manufacturing dosage forms for children from their birth to 18 y of age to develop age-appropriate pediatric dosage forms [22].

The European Paediatric Regulation, "Better medicines for children", went into effect in January 2007, intending to significantly increase the number of pediatric medical products that are authorized. Due to this legislation, without considering children, it is impossible to apply for new drugs or authorization of a patent. According to the regulation, children must be involved from the time of the early drug development process. Even though knowledge of the new drug's effects is still developing, firms are required to create a pediatric investigation plan (PIP) and submit it after clinical phase I. After obtaining the PIP agreement from the Paediatric Committee (PDCO), only then the companies can apply for drug approval at the EMA. As per EMA, "A PIP requirement also applies when a marketing-authorization holder wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized and covered by intellectual property rights". This has significantly aided in the expansion of the production of medications for children, bringing the development of pediatric medications closer to that of adult medications. For off-patent drugs, the preparation and submission of a PIP are optional. In such a case, if the product is necessary for pediatric use, then the applicants may apply for a pediatric use marketing authorization (PUMA) and it will be benefited from 10 y of data protection [23].

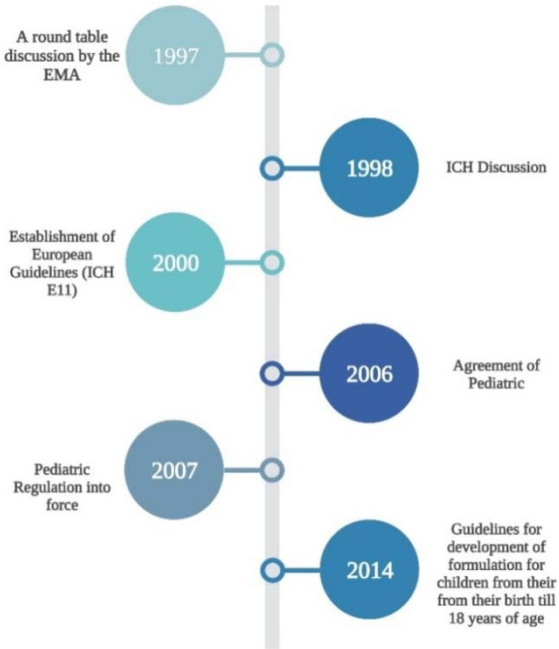

Fig. 2: Legislation of pediatrics in Europe [Authors creation] [17, 22]

India

In India, pediatric medications are developed based on adult human clinical studies and protocols. There are no rules unique to pediatric medication development. Clinical practice in India mainly relies on safety and efficacy data from other affluent nations or extrapolation from adult doses. Healthcare professionals and caregivers must

estimate the dose (either for therapeutic use or for carrying out clinical trials) by crushing tablets, cutting tablets into quarters or halves, opening capsules, or if it is a liquid, by proportionally reducing volume due to the lack of pediatric-specific guidelines. This method of medication administration is challenging and might lead to erroneous dose, which could diminish efficacy (due to under-dosing) or jeopardize safety (due to over-dosing) [24].

Oral solid dosage form

The solid dosage form (SDF) for oral use is the final drug product that is taken through the mouth, dissolved in the digestive tract, and delivered to the body through absorption into the bloodstream. They provide several advantages over other dosage forms especially liquid formulations, including long-term stability, precise dose, ease of transportation and handling, and low manufacturing costs, satisfying the basic goal of making a single-unit dosage form more versatile [25, 26]. They allow the modification of drugs, minimize the frequency of drug administration and pharmacokinetic parameters, and improve drug compliance. Although the solid oral dosage forms have the aforementioned advantages, they are not preferred in pediatrics to avoid the risk of inhalation or choking of the dosage form by the pediatric patient. Another disadvantage of the traditional SDF is the lack of dosage flexibility [27]. To address these problems, a two-way methodology can be used, including improvement in the development of dosage forms for the particular population and finding an innovative device for drug administration [6]. Smaller capsules and tablets are gaining traction as a viable alternative to traditional solid dosage forms, providing for more dose flexibility and, as a result, easier ingestion. According to a few published studies, solid dosage forms can be swallowed by children from the age of 6 mo when trained appropriately [28-30].

Flexible solid oral dose forms have been deemed the best dosage form for children by the World Health Organization (WHO) [31]. The dosage forms included are orodispersible, chewable, and soluble tablets. These dosage forms alleviate the stress of swallowing as they are intended to disperse in mouth or liquid before swallowing. These flexible solid oral dosage forms hold advantages against both conventional liquid and solid dosage forms because of ease of swallowing, flexibility in dosing as compared to liquid formulations, and lower production cost and stability in comparison to solid dosage forms. The LENA (Labelling of Enalapril from Neonates up to Adolescents) initiative was collaboratively launched within Europe to promote the development of flexible solid oral dosage forms. The LENA project's objective was to create and clinically assess a novel, age-appropriate solid oral enalapril formulation. A unique formulation of enalapril orodispersible minitablets (ODMT) has since undergone numerous advancements with the possibility of being eligible for a pediatric use marketing authorization (PUMA) [32, 33].

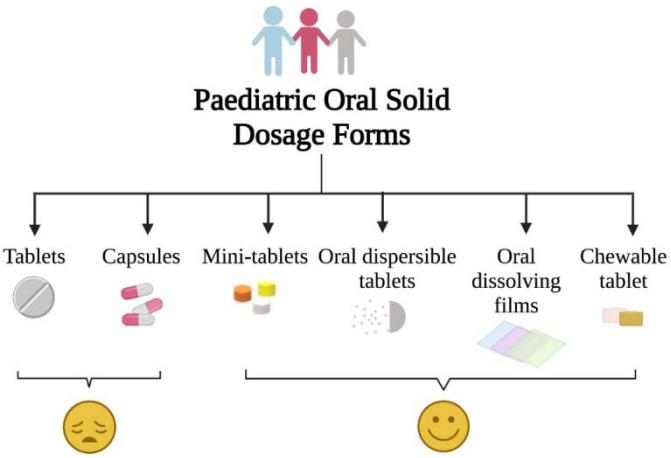

Fig. 3: Illustration of different types of solid dosage forms for pediatrics [Authors creation]

Minitablets

Minitablets can be defined as a type of solid oral dosage form that has a diameter of less than or equal to 3 mm. Mini tablets fall under the criteria of multi-particulate drug delivery systems which also include granules and pellets because they are composed of several discrete units. Due to their multi-unit composition, they offer the advantage of dose flexibility as well as they can be enclosed in a capsule or can be compressed into larger tablets thus avoiding the need to take multiple tablets [33]. They are in form of the coated and uncoated conventional type of mini-tablets and oro-dispersible mini-tablets. For patients with swallowing difficulty, these oro-dispersible minitablets are helpful as they show a very rapid disintegration directly in the mouth [34]. They are one of the recent advances in tablet formulations and are suitable for a wide range of populations including pediatrics, patients with problems related to swallowing, and geriatric patients. Orally disintegrating mini tablets (mini ODTs) have acquired widespread acceptance since the European Medicines Agency (EMA) established guidelines for creating formulations that are age-appropriate [35]. A particularly promising drug delivery method for giving individualized doses based on age, weight, and the condition is the use of mini tablets. Minitablets were formulated to make it easier for pediatric patients to take their drugs. Several studies have found that infants aged 6 to 12 mo may comfortably swallow a single 2 mm minitablet. Minitablets can be easily manufactured as modified release formulations such as delayed, extended, bimodal, pulsatile, and gastro-targeted using various techniques such as compression, hot melt extrusion, and 3D printing [23]. Problems with polypharmacy therapy and/or frequent dosing could be lessened by combining mini tablets with various active ingredients and/or release characteristics [36]. Despite this, the effective dose delivered by single minitablets is limited due to their small size. Desitin® minitablets (levetiracetam), Porfirio® (sodium valproate sustained release), KALYDECO® (ivacaftor), and LAMISIL® (terbinafine hydrochloride) are a few examples of marketed products [37].

Other multi-particulate systems such as granules and pellets are solid and hence do not require stabilizing agents thus eliminating the use of excessive excipients. They can be encapsulated in capsules or sachets and can be reconstituted in liquids such as water, fruit juices, milk, or in soft food substances. Though co-administering with food masks, the unpleasant taste of drugs and increase the patient adherence to the medicine, the absorption and bioavailability of the drugs vary and the therapeutic effect is affected. Sometimes even specialized equipment and accessories may be required for aiding in the administration of drugs, thus increasing the cost [33, 38]. Dhananjay *et al.* developed a method of taste masking using a hot melt extrusion technique for pediatrics without the loss of bioavailability. They used eudragit EPO as a taste-masking polymer, prepared granules, and later compressed them in tablets to make a solid dosage form with a flexible dose for pediatrics [39].

Oral dispersible tablets

Orally disintegrating tablets are gaining popularity among pediatric patients and health care professionals as they show increased patient compliance. Oral dispersible tablets (ODTs) are known as mouth-dissolving tablets, Oro dispersible tablets, fast-disintegrating tablets, melt-in-mouth tablets, Rapid melts, and rapid-dissolving tablets. ODTs show enhanced clinical effects as compared to conventional tablets because they disintegrate in the mouth and have pre-gastric absorption from various places of the esophagus. They show higher bioavailability because they bypass the hepatic first-pass metabolism. They have become a popular choice for pediatric patients due to their ease of administration, accurate dosing, increased palatability, rapid onset of action, better bioavailability, and cost-effectiveness [36]. The ODTs provide the advantage of improved swallow ability and stability profile as well as eliminating the use of functional excipients such as preservatives in the formulation. However, they posse the disadvantage of limited dose flexibility [33].

Oral dissolving films

Oral dissolving films (ODFs) on application to the oral cavity or placed on the tongue, hydrate because of the water-dissolving polymer which aids in immediate hydration of the dosage form by the saliva, adherence to the oral mucosa and causes disintegration of the dosage form followed by dissolution and release of drug and absorption of the drug from the oral cavity [40]. ODFs are prepared using the solvent casting method and consist of a polymeric matrix with a medication inserted in it. Alternative methods for the preparation of ODFs are, hot-melt-extrusion (use of solvents is avoided), electrospinning, or ink-jet printing. Regardless of the manufacturing process, ODFs' decreased size (2-9 cm2) and thickness (25 m to 2 mm) severely limit the amount of medicine that can be incorporated into them (usually 60-70 mg). Although novel technologies can combine higher medication dosages of>100 mg, this amount is still limited and so only potent drugs with specified physicochemical features can be properly delivered [41]. Devendra Singh Lodhi *et al.* in their review described the preparation of a xanthine and bronchodilator drug in mouth-dissolving films for asthma treatment using the transdermal patch technology. The oral films are a more efficacious formulation in the delivery of drugs and hence are helpful and preferred for children with asthma. [42]. Shruthi B. K., *et al.* prepared a mouth-dissolving film of levocetirizine hydrochloride using natural polymers by solvent casting method. The film was of the required thickness with a disintegration time of 14.28±1.52 sec and a drug release profile of 98.24%. This formulation showed the least disintegration time and highest drug content release as compared to the formulations with other natural polymers used in the study, thus being a preferred choice of formulation for pediatric patients [43]. The ODFs have gained immense potential as a patient-compliant dosage form in recent years. They are preferred over fast-dissolving tablets because of several advantages and hence, these are even given to schizophrenic and dysphasia patients. The advantages like ease of swallowing, accurate and convenient dosing, the absence of a requirement of water during administration, hepatic first-pass metabolism bypassed, rapid onset of action with enhanced bioavailability, and cost-effectiveness make ODFs a preferred choice [44].

Chewable tablets

Chewable tablets are designed to be first broken down into smaller particles and chewed by the teeth before ingesting them. They are intended to have easy disintegration in the mouth and are characterized to have a smooth texture and pleasant taste on disintegration. They are one of the easy, convenient, and favored types of dosage forms in pediatrics and geriatrics due to their ease during the administration and swallowing, pleasant taste, easy and good absorption, can be administered with water, and cost-effectiveness [45]. Along with chewable tablets, soft chews, and chewing gums also form a part of chewable formulations. Chewable products do not offer dose flexibility and are poorly suited for taste masking and controlled drug release. According to the available data, chewable tablets are secure and well-tolerated by kids 2 y of age and older. It should be warned, though, that these products might be misapprehended for confectionaries. The preparation of chewable tablets is done by compression and using patented technology without including the disintegrating agents [6].

Excipients in the pediatric formulation

Excipients are natural or synthetic materials that are used as functional or non-functional components in dosage forms with active ingredients. They make up nearly all dosage forms for human and veterinary usage, accounting for over 90% of the total weight of each drug. Excipients represent 0.5% of the global pharmaceutical market, around four billion dollars, according to industry analysts. They are used in pharmaceutical formulations as wetting agents, volume or weight extenders, diluents, emulsifiers, taste enhancers, preservatives, and solvents. They also serve as absorption enhancers. Excipient selection for the pediatric formulation is a crucial and tough task that requires the evaluation of several factors so that they are acceptable to use in the formulation. The preparation of a consistent dosage form depends prominently on the selection of excipients [46].

Excipient metabolism is influenced by various factors like weight, age, improper organ system development, the absence or presence of certain enzymes, and their numbers appearing in the pediatric population [5]. Rapid growth and development in children cause changes in the composition of lipids and fluids in the body, also, as changes in various body organs, binding of drugs to body proteins, active transport mechanisms, and metabolic pathways. The oral dosage form, the preferred route of administration, may not always be appropriate or readily available in dosages suitable for kids. To offer safe, efficient, and consistent dosages, dosage forms like pills and tablets are regularly adjusted in ineffective ways. Healthcare professionals and compounding pharmacists can be of assistance; however, the results might be variable because of different approaches. Additionally, these services might not always be accessible, especially in underdeveloped nations. Patients regularly employ strategies including division of doses, dissolving of drugs by crushing in liquids such as water and administering medications at levels that are not thoroughly evaluated.

The selection of safe excipients for pediatric dosage form formulation is not only an important phase but also one of the difficult processes because the excipients that are routinely used in dosage form for adults may not be as safe when taken in children, even at proportionate (lower) amounts because the pediatric population is physiologically distinct from the adult population in several respects [7, 47]**.** The physiologic factors influence the bioavailability of drugs through the processes of absorption, distribution, metabolism, and excretion (ADME). The effect of the physiological factors, according to a study state that, neonates have a prolonged stomach emptying time which is unpredictable and challenging to calculate. This prolonged stomach emptying time may cause more medication degradation because it increases the time spent in contact with the gastric contents. The enzyme activity of the pancreas is low in youngsters but increases as they grow thus affecting the bioavailability of enzyme-sensitive drugs. In newborns, the absorption of lipid-soluble drugs may reduce due to lesser bile acids and lipase release [5].

Considering all the aforementioned factors, a global database like the Inactive Ingredient Guide of the United States Food and Drug Administration (US FDA), the Center for Drug Evaluation and Research (CDER) is desperately needed towards clarifying authorized excipients and dosages in products intended for acute or chronic dosing in children [48]. The EMA guideline serves as a decision-making tool for assessing the safety profile of excipients [22]. In the pediatric formulation, the excipients must be to be inert, safe, and of the required quality. However, the necessity of excipients does not undermine their toxic effects. A study by Georgi and colleagues discovered that many pediatric medications contained some noxious and possibly harmful excipients for the pediatric population, as evidenced by the data found in two-thirds of newborns in 21 European countries [7]. In partnership with the (NICHD) National Institute of Child Health and Human Development and Pediatric Formulation Initiative of the U. S., the European Pediatric Formulation Initiative recently created the Safety and

Toxicity of Excipients (STEP), a Pediatric database that compiles information about the toxicity and safety of excipients used for pediatrics. The selection of palatability and solubility of appropriate excipients must be taken into consideration when developing both adult and pediatric formulations, including age-related safety profiles for selected excipients in pediatrics and younger neonates [48]. Excipients that form a part of the pediatric formulation are discussed in the following section.

Fig. 4: Excipients used in the formulation of pediatric solid oral dosage forms [Authors creation]

Diluents

Diluents are fillers that are utilized to augment the bulk content in the dosage form when the active element to be integrated into the formulation is insufficient. Diluents such as lactose, starch, and microcrystalline cellulose are frequently employed [7]. The objective of selecting diluents is, they are the agents that are used to increase bulkiness, cause better cohesion, improve the flow of the powder or granules during the preparation of dosage form, and aid in direct compression manufacturing.

Lactose is used as a filler that is commonly used in the manufacturing of capsules, tablets, lyophilized powders, and powder inhalers. Children and infants sometimes, show hypersensitive reactions to lactose. In lactose-intolerant infants, the metabolism of lactose does not occur efficiently due to a lack of the lactase enzyme, resulting in lactic acid accumulation causing gastric complaints as well as systemic symptoms. Other diluents like dehydrated calcium hydrogen phosphate, starch, cellulose powder, and erythritol may be used in the pediatric formulation as an alternative to lactose, owing to the similar flow and disintegrating properties as that of lactose [7, 49].

Starch acts as a versatile excipient because it has many properties and hence is used for various purposes such as diluent, binding agent, and disintegrating agent in solid dosage forms [2]. However, starch needs to be stored in a dry environment as it is prone to microbial conditions [50].

Microcrystalline cellulose is available as a white crystalline porous powder and is odorless. Chemically, it is pure cellulose that has been partially depolymerized. It is regarded as a material that is largely non-toxic and non-irritating and has a low risk of toxicity since, following oral administration, it is not absorbed systemically. Microcrystalline cellulose acts as a disintegrating and lubricating agent in the preparation of tablets and as a binder, thinner and lubricating agent in the formulation of tablets and oral capsules [7]. Shohei Nakamura, Chisato Tanaka, *et al.* documented the use of microcrystalline cellulose as an agent that aids in having a uniform distribution of the drug. They have also indicated that it may be used as a segregation inhibitor in formulations for children that contain a small amount of the drug which can be further formulated into mini tablets [51]. Dang zhang, Alfred C. F. Rumondor *et al.* have developed minitablets for pediatrics using microcrystalline cellulose. It was used during compression due to its ability to give tablets of uniform content of the drug [52].

Coating agents

Coating agents are the agents that are used to apply a coat over the surface of the dosage form to acquire desired qualities thus improving the acceptability and palatability of the drug. The coating also makes it easier for the patient to swallow the solid dosage form, enhances the stability of the product, protects the dosage form against the gastrointestinal environment; increases the mechanical resistance of the dosage form, and allows the formulation of a dosage form with a modified release.

The main function of phthalates in pharmaceutical formulations is as a film-forming agent, coating agent, or plasticizer. Phthalate exposure during pregnancy has been related to birth defects such as the cleft palate and skeletal deformities in the developing fetus. It was shown that they could be extremely hazardous to the growth and reproduction of experimental animals. The CDER provided recommendations to the pharmaceutical sector on phthalate use in March 2012, titled "Restricting the Use of Specific Phthalates as Excipients in CDER-Regulated Products," due to the hazards posed by specific phthalates. In this recommendation document, it is advised to stay away from phthalates like DBP (Dibutyl phthalate) and DEHP (di-(2-Ethylhexyl) phthalate) [7].

Sweeteners

Sweeteners, which improve the flavor of the pharmaceutical product, have a major role in increasing the tolerance and palatability of oral pediatric formulations. The type of APIs and the requirement of flavoring agents influence the concentration and choice of the sweetening agents in the formulation [53]. Sweeteners have been associated with photosensitivity responses, diarrhea, and insufficient nutritional absorption [7]. In the case of diseases like severe renal insufficiency and diabetes, an analysis of risk-benefit must be performed to ascertain the use of certain sweeteners and sugars because they pose numerous health and safety issues [53]. Sucrose, sorbitol, mannitol, aspartame, and sucralose are the most often used sweeteners in medicinal formulations [7]. Classification of Sweeteners is done as natural sweeteners and artificial sweeteners.

Numerous pharmaceutical oral formulations use natural sweeteners. They are high in calories, and as they move through the body, they metabolize and alter. Sucrose and fructose are the two natural sweeteners that are employed in pharmaceutical product composition the most frequently [53].

Sucrose is a naturally occurring disaccharide called that is digested into the monosaccharides, fructose, and glucose in the intestine. The use of sucrose must be avoided in the development of a formulation for children suffering from Type-1 of diabetes. High amounts given daily have also been said to be carcinogenic [7]. Another monosaccharide that is used as a sweetener is fructose. Children with diabetes should avoid it since it raises blood glucose levels. A reduction in the absorption of API along with laxative effects can be seen when used in high concentrations [53].

Artificial sweeteners are made from chemicals that are either synthesized or taken from naturally occurring elements and treated further. They have a high sweetening capacity and show a comparatively good profile of safety than natural sweeteners, so they may substitute sucrose like natural sweeteners in pharmaceutical formulations [53]. Aspartame is a synthetic sweetener that is frequently used in food products, as well as adult and pediatric dose forms. Aspartame consumption rises in oral disintegrating tablets and chewable medications. It is nearly 200 times sweeter than sucrose. Phenylalanine is extremely dangerous to phenylketonuria individuals as well as pregnant women carrying a fetus with this metabolopathy. Patients with phenylketonuria should refrain from consuming aspartame. Neurological (neurotoxicity, epilepsy, headache, panic attack, and hallucinations) and hypersensitive (vascular and granulomatous panniculitis) reactions, as well as a cross-reaction with sulfonamides, are among the side effects of aspartame that have been reported [54].

Sorbitol even though is a laxative in high dosages, it is safe for pediatric kids because it is a monosaccharide that is not absorbed by the digestive system. Additionally, it is used as a capsule plasticizer and diluent. Sorbitol may result in gastrointestinal problems such as nausea, vomiting, osmotic diarrhea, stomach pain, swelling, and flatulence. Sorbitol should be avoided in children with hypoglycemia and fructose intolerance since it is converted to fructose in the body. In rare instances, it might result in liver damage, a coma, and even death. Babies who accumulate sorbitol may develop retinopathy and cataracts because of their diabetes. Sorbitol content in pediatric formulations has been limited to 0.3 mg/kg [49, 54, 55].

Mannitol is both a diluent and a sweetener. It's been linked to severe allergic reactions in children. Like sorbitol, it is not absorbed by the digestive tract, and large amounts of it have laxative effects [7]. A chlorinated sugar called sucralose was created in 1976 by British researchers Tate and Lyle [53]. It has a sweetening power of 100 to 300 times sucrose [7]. Sucralose is the only sweetener that does not have calories and hence is known worldwide as a zero-caloric sugar alternative [53]. It can boost the expression of two cytochromes P450 isoforms, which are both necessary for the drug purification process, as well as the cell flow transport protein glycoprotein P and glycoprotein P, and hence cannot be considered completely inert. It alters the composition of the microbial flora of the intestine thus causing a reduction in the number of beneficial bacteria [7].

Coloring agents and dyes

The pharmaceutical, cosmetics, and food industries all use coloring compounds in various ways. Some of the purposes of coloring agents include customer attraction, product identification, and protection of things that are sensitive to light [56]. The majority of colorants used in oral pharmaceutical formulations fall into one of four categories: xanthene dyes (quinoline yellow), azo dyes (tartrazine) Triphenylmethane dyes (erythrosine), and dyes made from xanthene or xanthene derivatives [53]. Few colorants are universally acceptable from a regulatory standpoint since several coloring compounds have been associated with hypersensitivity and other unfavorable effects in children [53]. Asthma, urticaria, angioedema, hyperkinesis, and anaphylactic responses are the most frequent side effects associated with most dyes. A typical side effect of azo dye use in children is cross-sensitivity to indomethacin, sodium benzoate, and acetylsalicylic acid (ASA) [57]. As a result, it is advised that azo-dyes be avoided in pediatric drugs or that risk-benefit analyses be carried out before their inclusion in the formulation. Quinoline dyes are a common cause of contact dermatitis. Additionally, bronchoconstriction, skin rash, erythema, angioedema, and anaphylaxis may be brought on by triphenylmethane dyes. Xanthine dyes may cause photosensitization reactions in children and may also cause cancer [58].

Challenges in the development of pediatric dosage forms

The development of medication for pediatrics remains a significant issue for all stakeholders, including the pharmaceutical industry and international regulatory bodies [59]. Pediatric medication development faces many obstacles like a small and disorganized market, ethical as well as methodological restrictions for studies in pediatric patients, large research expenses, and a constrained and unreliable supply of data, which affect the development of pediatric drugs [4]. Along with challenges related to quality, safety, and efficacy of the pediatric dosage forms as well as physiological and formulation-related challenges, for any given drug, data for pharmacokinetic and pharmacodynamics, special attention is required in suiting the dosing requirements for all age groups and allow flexibility [57]. As a result of these difficulties, only a small amount of research has been done to tailor medicines to the needs of children [59]. Despite the large number of children affected in affluent countries, the pediatric market remains less. An estimated $20 million will go toward a pediatric development plan for a new pharmaceutical product, which might translate to a subpar, if not negative, return on investment for an already approved drug. Proposed legislation in the EU and the US intends to enhance children's overall health and well-being by extending pediatric pharmaceutical product research, development, and approval. It is unclear, nevertheless, if the current incentives would encourage more pediatric research in the pediatric age group in Europe as the patent extension period is not better than in the United States [60].

Pharmacological and physiological challenges

Pediatrics are not young grown-ups in terms of biological or pharmacological development. The pediatric patient population, on the other hand, does not belong to a homogeneous group and could be divided into sub-groups based on physiological (size and developmental biology) and pharmacological differences. They are divided into pre-term newborn infants (premature) of age less than 37 w, the full term newborn infants (neonates) of age 0 to 27 d, Infants and toddlers of age 28 d to 23 mo, 2-11 y children and adolescents from the age of 12 y to 17 to 18 y, the age varies according to the region, as it is 17 y for adolescents in the U. S. and 18 y in the U. K. [60].

Pre-term newborn infants

Extrapolating the efficacy of pharmaceutical drugs from adult trials is not viable (unless in exceptional situations). Even research with adult pediatric patients, however, could be challenging to apply to a pre-term newborn in a meaningful way (Guidance for Industry ICH E-11 2000). This population subset of the pediatric is not homogeneous, as shown by the huge developmental variations between an infant of 25-week gestation (0.5 kg) and a considerably bigger newborn of 30-week gestation newborn weighing 1.5 kg. Rapid changes in pharmacology and physiology, demanding distinct dose regimens, are major developmental biological and pharmacological things to consider while delivering drugs to pediatric patients that are pre-term; the incomplete renal development and hepatic clearance processes, as well as the BBB (Blood–Brain barrier) (it contains the capability for any medicines administered, not just those with high CNS permeability in adults, to pass into the CNS; Protein binding and displacement difficulties (especially bilirubin); chances (often unintentionally) for medication transdermal absorption; and specific newborn susceptibilities, such as retinopathy [60].

Full-term newborn infants

Full-term newborn infants are a group like preterm newborn infants, but more mature. Due to the competitive binding between albumin and bilirubin that is exhibited in newborns, medications that exhibit significant protein binding in adults are frequently more readily available in these patients. Because the blood-brain barrier is still developing, bilirubin (the levels are elevated in neonates) displacement can result in CNS damage. The mechanisms of renal and hepatic clearance are quickly developing in this pediatric subgroup. Drug concentrations and efficacy must be continuously evaluated and possibly modified on a day-to-day basis, with drugs like phenytoin and phenobarbital. Hepatically cleared medicines are extracted more slowly as a result. Drug distribution volumes in young pediatric patients may vary greatly from those in older pediatric or adult patients because of their ratio of higher surface area to weight, body water content, and fat content. Hence, the water-soluble medicines dissolve, in neonates to a larger extent, perhaps necessitating a higher dose to achieve the required plasma concentration [60]. The oral absorption of the drug is also difficult to predict in this class of infants as the gastric pH is higher than a majority of Caucasian adults and an increase in the absorption of acid-labile drugs is seen. These are a few factors that need to be considered during the development of dosage forms for pediatrics [60].

Toddlers and infants

The infants grow and mature rapidly during this period. As there are individual differences in organ maturation rates and physical growth a considerable subject intrasubject variability is seen. As the child becomes 23 mo old, the oral absorption is improved significantly, and the gastric pH as that of an adult is reached. The clearance mechanisms mature quickly (a considerable subject intrasubject variability is seen), with clearance (measured in mg/kg) frequently surpassing what is seen in adults. The reason is, that relative to total body weight, the liver in children is up to 50% larger than in adults. Therefore, compared to adult doses, hepatically cleared pharmaceutical dosages may need to be increased. During

infancy and the early years of childhood, the rates of gastric emptying and overall gut motility decrease [60].

Children

In this sub-group, most of the clearance pathways are like that of adults. Nevertheless, values of clearance frequently surpass the levels in adults and often rely on the maturation of metabolic processes. The surface area to weight ratio is more in neonates and young children as compared to adults, who have a thicker stratum corneum. Therefore, there is a larger chance of severe systemic exposure and associated side effects with topical drug delivery. In the research conducted by this subgroup, the effect of drugs on growth and development is of special importance. Children carrying out academic activities may experience difficulties with their psychomotor abilities and with the efficacy endpoints when taking CNS-active drugs. To monitor the effects of the drug on the child, developmental endpoints such as growth, weight gain, and academic achievement can be considered [60].

The efficacy of metabolizing enzymes can be affected by puberty and hence, a significant change may be needed for the dose that is administered based on mg/kg, of drugs like theophylline. It is required to study the effect of puberty on medical products and biological markers to indirectly evaluate the effect of the drug [61].

Adolescents

The impact of any dosage form on the physical, mental, and sexual development of this pediatric sub-group needs to be assessed since hormonal changes are significant in this age group. Hormonal shifts can affect the frequency and severity of several illness states, such as asthma and migraines. The ADME of the drug, as well as the needed dose, can be affected by biopharmaceutical differences between adults and children. Midazolam, for instance, shows a higher risk of side effects in children suffering from congenital heart disease and pulmonary hypertension, because smaller dosages than what is indicated are required on a strictly mg/kg basis. Gabapentin, on the other hand, requires higher doses in children under the age of five to control seizures. Similarly to this, the dosage of etodolac used to treat childhood rheumatoid arthritis must be increased by 2 to 3 times on an mg/kg basis [60]. Therefore, the age of the patient and their pharmacokinetics need to be considered during the development of a dosage form for pediatrics.

Formulation related challenges

Most medications are prepared in the form of solid oral dosage forms, typically tablets and capsules (NF-14) but a substantial percentage of pediatric and geriatric populations faces problem in swallowing these dosage forms (dysphagia). Hence, to overcome this challenge, oral dispersible tablets, oral dispersible films, mini tablets, and chewable tablets are developed. In the initial stages of the development of novel pharmaceuticals intended for oral administration, the property of a compound is seen for its suitability for an adult dosage form. It is examined for its compatibility to be formulated in a capsule or tablet dosage form. It has become important to check the compatibility and toxicity of the excipients that are to be used in the formulation and formulate a 'child-friendly dosage form' after the unfortunate 'Diethylene glycol poisoning' incident, that occurred a few years ago. Currently, there are well-established safety data on existing excipients, however, novel excipients must pass stringent animal safety testing before they are utilized in clinical trials. However, the toxicity of several common excipients, such as lactose, that are used presently may differ between pediatric and adult patients as well as among juvenile subgroups. Animal safety research generally helps in determining the maximum amount of dose that can be tolerated. Maximum tolerated doses for excipients are determined by animal safety research; however, these doses are not directly applicable for use in children as they are generally recommended for adult use [60].

Based on the data collected by a survey conducted by Elisa A., Francis B., Mariagiovanna S., *et al.*, children preferred liquid as a dosage form over other dosage forms like tablets, oro-dispersible films and tablets, chewable tablets, and so on. However, liquid dosage forms have some limitations such as the inclusion of excipients to enhance the solubility of the active ingredients, preservatives, and surfactants which may be harmful to children. There is the possibility of non-uniform dosing and maintenance of stability can be a problem in liquid formulations. They even tend to be more expensive as compared to the oral solid dosage forms and hence can be less accessible to the less economically developed class [1, 62]. In the year 2008, the World Health Organization (WHO) encouraged the development and prescription of flexible solid dosage forms over liquid formulations as a preferable oral dosage form for children [31, 63]. However, oral solid dosage forms are a cause of concern for pediatric patients due to the fear of choking. Hence several studies were carried out on the development of novel dosage forms such as mini tablets, which have demonstrated the ability of young pediatric patients to administer these dosage forms safely (1). Klingmann *et al.* exhibited that administration of numerous mini tablets was practical, well tolerated, superior to syrup, and secure for all children 6 mo and older [3]. The selection of such advanced formulations is limited due to various reasons such as less national market, limited availability or accessibility, higher cost than the conventional oral solid dosage forms, or the fact that the prescribers are still accustomed to prescribing conventional dosage forms over these, in children [31, 63, 64].

One of the important factors affecting the compliance of pediatric patients is taste. Therefore, when obnoxious-tasting drugs are given to the pediatric patient, they are generally given by mixing them with fruit juices or with food. Even though it might mask the flavor of the tablet, this could harm its effectiveness and safety for several reasons, such as improper dosing and changed bioavailability. Unfortunately, one of the most significant formulation issues with major drug substances is undesirable palatability [60]. The use of flavoring agents, sweetening agents, amino acids, coating agents, and polymeric materials has all been used to address this issue. However, doing taste studies on healthy children may raise ethical concerns. Theoretically, healthy children should not be registered as healthy volunteers because they cannot give their consent and are vulnerable in the same way that children with illnesses or disorders are, this is according to the European Ad hoc committee on ethical concerns of clinical studies in minors. An exception might be made for healthy kids who take part in palatability tests, such as swill and spit taste tests for new flavors of drugs (European Economic Area, 2008). Using healthy volunteers, in the "swill and spit" method, for testing numerous medications, including cytotoxic drugs will be unethical. When given to kids with an ailment that must be treated, the taste should be assessed, and ideally, the study will be incorporated into another clinical trial. Taste can be evaluated during successive doses contrary to the studies carried out on single administration in volunteers.

Toxicity of excipients in pediatric dosage form

It is well known that excipients can interact with cellular molecules to trigger unpleasant reactions or can induce effects that are incompatible with the API. The interactions of the drug with an excipient, excipients with an excipient, or interaction with cellular molecules and the excipients can have serious effects on pediatric patients and frequently interfere with healthy growth and development [49].

Clinical trials for oral solid dosage forms for pediatric patients

Clinical trials should be publicly registered to safeguard participants from pointless or redundant experiments, increase transparency, and prevent publication bias and selective outcome reporting [17, 68-71]. Regulatory agencies, ethics committees, and journals all strongly support prospective trial registration as a requirement for publishing [71]. An examination of available pediatric randomized controlled trials, however, revealed that several of them had insufficient and poorly reported data on adverse medication reactions [68, 72, 73]. Public trust and confidence in pediatric research are increased when unbiased results, even negative ones, are promptly and openly published. This is necessary for pediatric trial results to be applied in clinical practice [74-76]. Due to the paucity of pediatric patients with the same medical issue as under study, clinical trials in these patients can be a problem. Furthermore, it is difficult to convince parents to allow their children to be a part of clinical studies. Another challenge

that occurs is performing clinical trials for a novel formulation developed by pharmaceutical industries for children, with modified release profiles, as it is in a concentration not suitable for the patients or may contain certain excipients that are not suitable for children of a particular age group [77].

Finding a balance between the necessity of conducting trials to safeguard children from the risk of ingesting untested medications and the need to protect children from unknown risks and damages that may arise by participating in trials is challenging [82-85]. The same moral standards that apply to adult cases—respect for persons, beneficence, non-maleficence, and justice—apply to cases involving minors. The inability of children to comprehend the hazards associated with trials and dependence on adults to make decisions for them present extra ethical issues [68, 82]. Since then, an independent board of safety monitoring that can comprehend the unpredictable and special nature of responses in children is required. Trial governance is also getting stricter [68, 83, 84]. Long-term monitoring is required in children because several adverse outcomes could manifest in later life [68, 84, 85]. The clinical studies conducted for pediatric oral solid dosage forms are discussed in table 3. The search for clinical trials was done using a database such as clinicaltrials. gov with keywords such as pediatric solid oral dosage forms, pediatric dosage forms, and so on. The data were analyzed and only relevant data about the clinical trials for children were included in the review.

Table 1: Toxicity of excipients

Excipient	Major use	Toxicity	Reference
Sucrose	Sweetener	Decay of Tooth Carcinogenicity, degradation of the active drug, increased degradation of active drug, allergic responses (a rare occurrence)	[53, 65, 66]
Aspartame	Sweetener	Headache, loss of memory, grand mal seizures, memory loss, gastrointestinal issues, dermatological symptoms (Observed to occur in large amounts), Cross-reactivity with sulfonamides and Phenylketonuria.	[53, 65]
Saccharin	Sweetener	Irritability, insomnia, carcinogenicity cross-sensitivity with sulfonamides, opisthotonus, and strabismus.	[53]
Sucralose	Sweetener	Carcinogenicity and diabetes disease.	[53]
Sorbitol	Sweetener	Large amounts: osmotic diarrhea	[65]
Azo dyes	Coloring agent	Urticaria, hyperkinesis, angioedema, asthma, anaphylactic reactions, and cross-sensitivity are observed with drugs like indomethacin, sodium benzoate, and acetylsalicylic acid.	[65]
Quinoline dyes	Coloring agent	Contact dermatitis	[65]
Triphenylmethane Dyes	Coloring agent	Angioedema, Bronchoconstriction, erythema multiforme-like skin rash	[65]
Xanthine dyes	Coloring agent	Carcinogenicity	[65]
Peppermint oil	Flavouring agent	Muscle pain, Cooling or burning sensations, atrial fibrillation.	[53]

Table 2: Marketed dosage form

Type of dosage form	Route	Active ingredients	Excipients	Dose	Marketed name	Company	Therapeutic use	References
Chewable tablet	Oral	Amoxicillin trihydrate	Aspartame, Povidone, Magnesium stearate mannitol, Cherry banana peppermint flavorings, Red 40 aluminum lake	25 to 40 mg/kg/day up to 875 mg twice a day or 20-40 mg/kg/day	Amoxil	Glaxo smith	Antibiotics (treat bacterial infections)	[67]
Chewable Tablet	Oral	H-dibenzo [b,f] azepine-5-caroxamide	Gelatin, glycerol, flavors, silicon dioxide, sodium starch glycolate, magnesium stearate, sucrose, and stearic acid.	Less than the age of 6 y: 10–35 mg/kg/day 6-12 y 50 mg	Tegretol	Novartis	Treat epilepsy	[67, 123]
Chewable tablet	Oral	Cetirizine HCl 5 mg, pseudoephedrine 120 mg	Acesulfame potassium, artificial grape flavor, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, mannitol	2-5 y: 2.5 to 5 mg per day, 6 to 11 y: 5 to 10 mg per day	Zyrtec 1	Pfizer	Antihistamine, nasal decongestant	[67]
Chewable tablet	Oral	Lamotrigine	Blackcurrant flavor Calcium carbonate ($CaCO_2$), Magnesium stearate, sodium saccharin, Low-substituted HPC Magnesium aluminum silicate, povidone, sodium starch glycolate	2, 5, or 25 mg	Lamictal	SKB	Anticonvulsant/anti-epileptic	[67]
Chewable tablet	Oral	Methylphenidate hydrohloride	Aspartame, Maltose, Microcrystalline Cellulose, Grape Flavor, Guar Gum, Pregelatinized starch Stearic acid.	5 to 60 mg b. i.d.	Methylin1	Alliant pharmaceuticals	Increase attention and decrease impulsiveness and hyperactivity in patients with ADHD	[67]
Chewable tablets	Oral	Montelukast	Mannitol Microcrystalline cellulose HPC, Croscarmellose, sodiumCherry flavor, AspartameMagnesium stearate	4 mg q. d.	Singulair	Merck	Coughing caused due to asthma, breathing difficulty, tightness of the chest, and prevention of wheezing. caused by asthma	[67]

Type of dosage form	Route	Active ingredients	Excipients	Dose	Marketed name	Company	Therapeutic use	References
Chewable tablets	Oral	Thiabendazole	Acacia, Calcium phosphate, mannitol, lactose, methyl cellulose, magnesium stearate, Sodium saccharin	30 lb: 250 mg	Mintezol	Merck	Anthelmintic	[67]
Chewable tablets	Oral	Thiabendazole	Acacia, lactose, Calcium phosphate, magnesium stearate, methyl cellulose, mannitol, Sodium saccharin, methacrylate copolymer, Risperidone, Aspartame, Bicarbonate of sodium, Colloidal silicon dioxide, ferric oxide, citric acid, Fruity flavor.	30 lb: 250 mg	Mintezol	Merck	Anthelmintic	[67]
Orally disintegrating tablets with delayed release	Oral	Lansoprazole	Microcrystalline cellulose, monohydrate lactose, hydroxypropyl cellulose, magnesium carbonate, Titanium dioxide, and Hypromellose.	Less than 30 kg: thrice a day 15 mg. Greater than 30 kg: Thrice a day 30 mg.	PREVACID	TAP/GERD	Heartburn, difficulty swallowing, and persistent cough.	[67]
Capsule	Oral	Atomoxetine	Pregelatinized starch Dimethicone	0.5 to 1.2 mg/kg up to 100 mg did.	Strattera	Lilly	Treat attention-deficit hyperactivity disorder (ADHD)	[67]
Tablet	Oral	Atorvastatin calcium, amlodipine besylate.	Microcrystalline cellulose, water, calcium carbonate, colloidal silicon dioxide, Polysorbate 80, croscarmellose sodium, pregelatinized starch, HPC.	6 to 17 y of age: 2.5 to 5 mg (amlodipine) q. d	Cadet	Pfizer	Lowering blood pressure and low-density lipoprotein cholesterol.	[67]
Tablet	Oral	Atovaquone and Proguanil HCl	Sodium starch glycolate, Povidone K30, Microcrystalline cellulose, Hydroxypropyl cellulose, Poloxamer 188, magnesium stearate	1–3 tablets q. d	Malarone1	GlaxoSmithKline	Prophylaxis of Plasmodium falciparum malaria.	[67]
Tablet	Oral	Busulfan	Lactose (anhydrous) Magnesium stearate Pregelatinized stark h	60 mg/kg did.	McLerran	GlaxoSmithKline	Chronic myelogenous leukemia	[67]
Tablet	Oral	Dextroamphetamine Sulfate	Corn starch, magnesium stearate, lactose, acacia, sucrose, Sodium starch glycolate is contained in a 10 mg tablet.	3 to 5 y: 2.5 mg per day, greater than 6 y of age: 5 mg per day	Petrostate	Shire US	To control symptoms of attention deficit hyperactivity disorder (ADHD;	[67]
Tablet	Oral	Fexofenadine hydrochloride	Pregelatinized starch, magnesium stearate, croscarmellose sodium, microcrystalline cellulose.	30 twice a day.	Allegra	Sanofi-Aventis	To relieve allergy symptom	[67]
Tablet	Oral	Irbesartan	Magnesium stearate, microcrystalline cellulose, Poloxamer 188, pregelatinized starch, croscarmellose sodium, lactose	6 to 12 y: 75 to 150 mg did. 13 to 16 y of age: 150 to 300 mg did.	Avapro	BMS	Treat high blood pressure	[67]
Tablet	Oral	Ivermectin	Microcrystalline cellulose, citric acid, pregelatinized starch, magnesium stearate, BHA.	Greater than 15 kg: 200 mg per kg one time dose	Tremetol	Merck	Symptoms of certain parasite infections	[67]
Tablet	Oral	Zafirlukast	Microcrystalline cellulose, Lactose, croscarmellose sodium, HPMC, povidone, titanium dioxide.	Twice a day 10 mg.	Accolate	AstraZeneca	Treat asthma	[67]
Tablet	Oral	Ranitidine	Sodium benzoate, sodium bicarbonate, aspartame, monosodium citrate, povidone.	2 to10 mg per kg up to 150 mg twice a day.	Zantac	GlaxoSmithKline	Treat indigestion, heartburn, acid reflux,	[67]
Tablet	Oral	Benazepril	Propylene glycol, microcrystalline cellulose, polysorbate 80, starch, Titanium dioxide, colloidal silicon dioxide, Hydrogenated castor oil, HPMC, magnesium stearate, lactose, talc, risperidone.	0.1 to 0.6 mg per kg every day, up to 40 mg daily	Lotensin	Novartis	Treat high blood pressure	[67]

Table 3: Clinical trials for solid oral dosage forms on pediatric patients

Clinical trial number	Description	Type of dosage form	Age of participants	Status of trial	Year (Trials Completed or results first posted)	Reference
NCT01196195	The study evaluates the pharmacokinetics, safety, efficacy, and acceptability of lopinavir/ritonavir tablets in children infected with HIV-1. The dose is decided by weight.	Tablets	Up to 18 y	Completed	2013	[86]
NCT04236414	A study was performed to investigate the safety, efficacy, tolerability, and pharmacokinetics of the tablet Olaparib in pediatric patients having solid tumours	Tablets	0 to 18 y	Recruiting	2020	[87]
NCT02650401	A trial still active is being performed to study Entrectinib (Rxdx-101) in children and adolescents with locally advanced or metastatic solid or primary CNS tumours that have no satisfactory treatment options.	Capsules and mini tablets	New-born to 18 y	Active	2016	[88]
NCT02956109	A clinical study was conducted to test the pharmacokinetics of a single dose of the drug Finerenone with tablets of 1.25 mg and 5x0.25 mg in comparison with a 10 mg tablet for adults.	Tablets	18 y to 45	Completed	2017	[89]
NCT02174874	An observational study was performed in children to show that orally disintegrating tablets of ondansetron were more efficient in controlling vomiting and diarrhea in the patients within 5 min of administration as compared to patients receiving ondansetron oral solution. The investigators hope to persuade healthcare professionals to use ondansetron orally disintegrating tablets for pediatric patients suffering from vomiting by demonstrating this increased tolerability.	Orally Disintegrating tablets	3 to 10 y	Completed	2014	[90]
NCT01004263	A study was performed to provide long-term tolerability and safety data on the use of the drug Rizatriptan benzoate in the form of orally disintegrating tablet in children and adolescents for its use in acute migraine in pediatric patients over a period.	Orally disintegrating tablets	12 to 17 y	Completed	2011	[91]
NCT02034162	A study to evaluate the safety and efficacy of mebendazole drug in the form of a chewable tablet.	Chewable tablets	1 to 16 y	Completed	2016	[92]
NCT01852812	A study was performed to provide appropriate exposure to montelukast drug in Japanese pediatric participants suffering from Perennial Allergic Rhinitis (PAR).	Oral granules, Chewable tablets	1 to 15 y	Completed	2014	[93]
NCT00534976	The study evaluates the ease of breathing after exercising in children on the administration of the Montelukast drug.	Chewable tablet	4 to 14 y	Completed	2011	[94]
NCT03650400	The study was performed to assess the pharmacokinetics of the drug Fevipiprant in pediatric asthma patients. The study results will allow the development of the dosage form in a dose suitable to the age group of the pediatric population.	Chewable tablet	6 to 11 y	Completed	2020	[95]
NCT01717287	A non-comparative study evaluating the safety, tolerability, and anti-retroviral activity of two dosage forms of Raltegravir in combination with other retroviral agents.	Film-coated tablets, Chewable tablets	2 to 17 y	Completed	2014	[96]
NCT00485264	To study the pharmacokinetics of the drug raltegravir in children and adolescents infected with HIV-virus.	Film-coated tablets, Chewable tablets, Oral granules for suspension	30 d to 18 y	Completed	2017	[97]
NCT00827606	A three-year trial to study the growth and development along with the efficacy of reduction in cholesterol levels in pediatric participants of the study suffering from familial hypercholesterolemia receiving treatment with the drug Atorvastatin.	Tablets, Chewable tablets	6 to 15 y	Completed	2013	[98]
NCT02004288	The study was performed to investigate the beneficial role of *Lactobacillus reuteri* in the treatment of pediatric patients with Anorexia nervosa who develop motility disorder. The study also evaluates the possible role of probiotics on nutritional recovery.	Chewable tablets	8 to 18 y	Completed	2016	[99]
NCT02644291	A Phase 1 trial to assess the safety and side-effects of mebendazole drug for the treatment of brain tumors in pediatric patients	Chewable tablets	1 to 21 y	Completed	2022	[100]

Patents

The patent landscape for pediatric oral solid dosage forms is discussed in table 4. The search for patents was done using the databases such as European Patent Office (Espacenet), World Intellectual Property Organization (Patentscope), United States patent and Trademark Office (USPTO), and Google patents, from the year 2018 to 2022, however, the review also contains patent during the year 2014 to 2018. The keywords combinations including liquid, oro-dispersible, chewable, pediatric dosage form, formations, and so on were used. The data was analyzed for relevance and only the patents relating to oral solid dosage forms for pediatrics, with claims of being favorable for children were included in the review.

Expert opinion

The drugs formulated for children should of the same quality, safety, and efficacy as that for adults. According to the statement by Harry Shirkey in 1963, pediatric patients are considered therapeutic orphans due to their unmet therapeutic needs of these patients. Expanding the range of pharmacological medicines that are age-appropriate is the new focus of research. The data collected in this review highlights the enforcement of new guidelines for the development of pediatric formulations, new advances in oral solid dosage forms, an improved situation of clinical trials, and an increase in the number of patents for these flexible dosage forms. The regulatory bodies have encouraged applicants to work on new dosage forms, devices used for the administration of flexible dosage forms, and the packaging of the formulations to improve patient acceptance and adherence, reduce dosing errors, and increase the drug solubility and permeability [120, 121]

The liquid oral dosage forms considered the most preferred and ideal dosage forms for children have slipped several spots in the hierarchy of preferred formulations, primarily because of problems with stability, solubility, storage, and transportation. The reviewed patents show an increase in flexible dosage forms. The patents

included in the review show an increase in flexible pharmaceutical formulations. The mini tablets are well accepted by children but due to their minuscule size, they indicate a need for dosing devices to facilitate handling and deposition of the formulation in the mouth as well as for accurate dosing.

As such, in addition to the use of flavorings and sweeteners, other taste-masking techniques have been used to mask the unpleasant taste of medications and these techniques include coating using a polymer and adjustment of the pH of the pharmaceutical formulation, along with other methods. At the same time, the choice of approved excipients should be made carefully to protect youngsters from exposure to potentially dangerous substances. The STEP (Safety and Toxicity of Excipients for Pediatrics) database, which provides information on the safety and toxicity of excipients, was developed through a collaboration between the European Pediatric Formulation Initiative and the United States Formulation Initiative in response to this need.

Safety issues, for instance, can develop when certain excipients, particularly preservatives, are used in pediatric formulations. Preservatives are typically thought to be acceptable for use in preparations for multiple doses, but limited information is currently available on the safe levels of exposure in pediatrics belonging to different age groups. Hence, there is a need to justify the appropriateness of the use of preservatives in the formulation for pediatrics in terms of the risk-benefit ratio. EMA encourages drug companies to adopt novel strategies to develop the preparation of pediatric formulations that are free of preservatives [121]. Therefore, a smooth transition to formulations devoid of preservatives could be supported by replacing multidose liquid formulations with single-dose solid dosage forms.

After about a decade of the declaration of related legislation and guidelines, the information about pediatric dosage forms is still limited. This is partly because of limited and indistinct evidence on the clinical trial methodologies and ethical restrictions for underaged participants. However, it is controversial whether the ethical and methodological challenges associated with conducting clinical trials in the pediatric population are worth the risk involved in the likelihood that untested drugs may subsequently be hazardous. Despite this, a 2.5-fold increase is observed in pediatric clinical trials over the period from 2007 to 2015, showing an admirable step in the right direction.

According to the author's opinion, in years to come, the pharmaceutical sector will adapt and overcome the challenges in new drug development leading to a quantifiable expansion of the age-specific market in the long term. There is a noticeable increase in the number of research projects and funding opportunities for the development of formulations suitable to pediatrics, and the development of pediatric research networks aims to encourage cooperation between regulatory bodies, academic institutions, and industry, as well as patient associations and healthcare providers, to share knowledge and bring scientists in compliance with the requirements of the regulatory agencies [121].

Table 4: Patents for pediatric solid oral dosage forms

Country code	Patent number	Title	Description	Year	Applicant/ Assignee name	*In vivo* studies	Reference
EU	EP2699094A1	Taste-masked formulations of raltegravir	It consists of coated API granules that are mixed with screened powder excipient blend in either tablet or sachet form.	2014	Merck Sharp and Dohme Corp	N/A	[101]
US	US20210346392A1	Pharmaceutical composition for oral administration	It consists of pharmaceutically acceptable salt for oral administration with rapid dissolution properties.	2021	Astellas Pharma Inc	N/A	[102]
US	US10034882B2	Tofacitinib orally disintegrating tablets	Taste-masked ODTs of reduced weight	2018	Unichem Laboratories Ltd	N/A	[103]
US	US9901546B2	Orally disintegrable tablets	ODTs with enteric-coated gran	2018	Takeda Pharmaceutical Co Ltd	N/A	[104]
US	US9861577B2	Orally disintegrable tablets	ODTs with improved properties	2018	Kyowa Kirin Co Ltd	N/A	[105]
US	US20180296479A1	Rapidly Dispersible Dosage Form with High Drug Content	3D printed antiepileptic ODTs	2018	Aprecia Pharmaceuticals LLC	PK	[106]
CN	CN107823153A	A kind of Amlodipine Besylate Tablet oral disintegrating tablet prepared using 3D printing and preparation method thereof	3D printed ODTs	2018	Jiangsu Huhong biomedical Co., Ltd.	N/A	[107]
CN	CN110269844A	A kind of preparation method based on ink-jet 3D printing olanzapine orally disintegrating tablet	3D printed ODTs	2019	Each Hong Industrial (shanghai) Co Ltd	N/A	[108]
AU	AU2020201762A1	Process for making tablet using radiofrequency and lossy coated particles	ODTs with radiofrequency and lossy-coated particles. The drug is acetaminophen	2020	Johnson and Johnson Consumer Inc	N/A	[109]
US	US20190175617A1	Dexamethasone oral film	Oral dispersible films with minimum excipients and a high load of drug	2019	LTS Lohmann Therapie Systeme GmbH and Co KG ACUCORT AB	PK and bioequivalence in healthy volunteers and hamsters	[110]
US	US20190380973A1	Taste-Masked Formulations of Raltegravir	Many taste-masked controlled release oral dispersible films in the process of manufacturing.	2019	Merck Sharp and Dohme Corp	N/A	[111]
US	US20190000766A1	Abuse deterrent soft chewable drug formulations	It states the development of oral, abuse-deterrent, edible soft chewable tablets to prevent damage due to human or animal subjects.	2019	First Time Us Generics LLC	N/A	[112]

Country code	Patent number	Title	Description	Year	Applicant/ Assignee name	*In vivo* studies	Reference
US	US20190350850A1	Taste masking product	Chocolate-based Chewable tablets	2019	University of Western Australia	A comparison of taste, pharmacokinetics, and pharmacodynamics that were given orally is done with intravenous administration in 150 pediatric patients (age: from 3 to 16 y)	[113]
US	US20200000716A1	Multicomponent gummy compositions with hardcore	It is a multi-component dosage system that is used to deliver one or more drugs to the consumer.	2020	Church and Dwight Co Inc	N/A	[114]
US	US20190060277A1	Melatonin mini-tablets and the method of manufacturing are the same.	Mini tablets with prolonged release	2019	Neurim Pharmaceuticals 1991 Ltd	Efficacy on 125 children	[115]
US	US20190105275A1	Oral pharmaceutical compositions of mesalazine	Extended or delayed release mini tablets.	2019	Ferring BV	N/A	[116]
AU	AU2019280026A1	Galenic formulations of organic compounds	Controlled-release Mini tablets for the treatment of heart failure.	2020	Novartis AG	Pharmacokinetics and the effect of food are observed in 39 healthy volunteers.	[117]
US	US9636304B2	A pharmaceutical composition comprising citrate and bicarbonate salts and use thereof for treating cystinuria	Mini tablets for cystinuria treatment	2017	Advicenne	Effect on urinary pH after administration to healthy adults	[118]
US	US20190274959A1	Pharmaceutical composition and administrations thereof	It includes the formulation of solid dispersions that are further processed into powders, granules, and mini tablets	2019	Vertex Pharmaceuticals Inc	N/A	[119]

CONCLUSION

The development of pediatric dosage forms has not been the primary focus of pharmaceutical industries; however, recent advances have been changing the scenario that has persisted over the years. The pediatric dosage form can be challenging to manufacture due to biological factors of the pediatric patients, the various physiological development stages of the pediatric population, that is, from newborns to young adults, physiochemical properties of the drug, its taste, and stability. These factors need to be considered during the manufacturing of the formulation for this population. The palatability of oral solid dosage forms is a significant factor affecting the adherence of a patient to the dosage regimen. There has been a strong motivation to move forward with palatability research after the New European Pediatric Regulation implementation. The smaller market size has also been a matter of concern that hampered the growth of pediatric formulations. The regulatory acts have provided guidelines for the development of pediatric formulations and performing clinical trials, thus promoting, and ensuring the preparation of safe dosage forms for children and less exposure to toxicity of dosage forms during the trials. The factors such as the route of administration of the formulation, excipients used, and the dosage should be made according to that of the pediatric population rather than comparing or taking the standards by referring to the adult dosage forms because even the approved drugs for adults can provide significant problems to children due to variations in the absorption, distribution, metabolism, and excretion of drugs and also may cause toxicity to the pediatric population. The pediatric projects in the U. S. and Europe are the two most significant programs addressing the issue of toxicity of excipients in pediatric dosage forms. As a part of this project, the STEP database was created that provides information about the toxicity, pharmacology, and safety of the excipients used in the pediatric dosage forms. Thus, helping in determining the most suitable excipient for a particular dosage form. The clinical trials in children are minimum due to the issues related to the toxicity of the excipients used in the formulation, and the inability of the population to give consent or to prevent the exposure of the pediatric population to the toxic effects of the dosage forms and the hesitation of the parents to allow their child to participate in clinical trials. However, by balancing the risk-benefit ratio and by informed consent, drafting an efficient clinical trial for children can aid in the formulation of an age-appropriate, most suitable dosage form for pediatric patients. The development of flexible dosage forms such as mini-tablets, chewable tablets, orodispersible films, and tablets along with modifications in conventional dosage forms may increase the preference of the pediatric population towards oral solid dosage forms.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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