

FORMULATING MEDICINES FOR CHILDREN: CHALLENGES AND ISSUES

The development of child-appropriate drug formulations still represents a challenge. It is clearly important to improve public-private partnerships that progress in creating technological platforms for developing pediatric formulations which allow better drug delivery and decrease of safety risks in child, in line with the guidelines of the regulatory agencies.



Children are commonly considered “therapeutic orphans” because the majority of medicines on the market have not been studied in the pediatric population, nor have been approved by regulatory authorities for use in children. For years, the lack of information on safety, efficacy and dosing of pediatric drugs, as well as the lack of child-appropriate formulations, resulted in the unsatisfactory treatment of pediatric patients [1]. Among others, the lack of children tailored formulations has a huge impact. *Ad hoc* formulations are necessary in order to deliver the right dose also assuring the right level of absorption, plasma concentration, metabolism and drug excretion. It also would remove the need to manipulate medicines, e.g. splitting tablets that are designed for adults into smaller fractions that provide the appropriate dose for children or using untested solutions of the existing forms.

So far, healthcare professionals had no therapeutic alternatives and often use off label medicinal products in children, with the associated risks of inefficacy or increased adverse reactions. This use is particularly high in case of ‘off-patent’ drugs (perhaps as much as 70%) but encompasses innovative drugs as well. The “pediatric off-label use” specifically includes all pediatric uses of a marketed drug not detailed in the *Summary of Product Characteristics*, with particular reference to therapeutic indication, appropriate strength (dosage by age), pharmaceutical form, route of administration. It is a widespread phenomenon in all the countries and in many therapeutic areas [2-4], and it has become an important issue for the safeguard of children’s health.

Current regulatory status

To fill in the gap, in the past decades, legislative and regulatory acts have been issued to promote the development and availability of medicines for pediatric patients. In particular, in Europe the Regulation on “medicinal products for pediatric use” (EC No. 1901/2006 [5] as amended [6]) has been released with the aim of assuring high quality research for pediatric medicines development, increasing the availability of information on the safe and effective use of medicinal products in the pediatric population, and avoiding unnecessary repetition of studies. According to the Pediatric Regulation, it is mandatory for pharmaceutical companies to prepare and submit a Pediatric Investigation Plan (PIP) to the European Medicine Agency (EMA) - Pediatric Committee (PDCO), when they plan to applying for a new Marketing Authorization (MA) or for any MA variation (including new indications, new pharmaceutical forms and new routes of administration). The introduction of the PIP in the legal European framework aims at ensuring that the pediatric development of any medicinal products becomes an integral part of the development program for adults. Moreover, it aims at ensuring that appropriate pediatric studies are performed to obtain the necessary quality, safety and efficacy data to support the authorization of a medicine for use in children. The absence of an approved PIP in a Marketing Authorization Application (MAA) will result in automatic rejection. A PIP shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets



of the pediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the pediatric population.

In case of an 'off-patent' drug, this obligation does not apply, but a specific voluntary MA procedure (the 'Pediatric Use Marketing Authorization'-PUMA) is foreseen. The PUMA benefits from 10 years data protection. Applications for PUMAs, which must contain the results from an agreed PIP, can refer to published literature and/or dossier data even if the product is only approved in one or more Member State and not in the whole community.

To increase the interest of Health Authorities, commercial sponsors and other interested parties in developing drugs for children, the EMA has released two important instruments:

- the list of the medicines of Therapeutic Interest for children, divided by therapeutic area, age of children and therapeutic indication;
- the list of 'priority' [7] for developing and funding medicines that are off-patent but that are used off-label in children due to their consolidated use and the recognized therapeutic interest.

Active substance	Therapeutic needs	Priority	PAED. Formulation needed	PK and/or PD needed	Efficacy/Safety needed
Allopurinol	2007			x	x
Amiodarone	2013		x	x	x
Atropin	2006				
Bisacodyl	2007		x		x
Carvediol	2013		x	x	x
Chloralhydrate	2006		x		x
Ciclosporin	2006		x	x	
Diclofenac	2005	x	x	x	x
Flecainide	2013		x	x	x
Hydrochlorothiazide	2014		x	x	x
Hydrocortisone ¹	2006		x	?	
Hydroxychloroquine		x	x	x	
Hydroxyurea			x		
Ibuprofen	2005		x	?	
Indomethacin	2006		x	?	
Isoniazid, rifampicin, ethambutol, pyrazinamide		x	x	x	
ketoconazole	2014		x	x	x
Ketoprofene			x		x
Lamotrigine	2007		x	x	x
Lithium	2007		x		x
Low molecular weight heparins	2013		x	x	x
Metoprolol	2013		x	x	x
Nifedipine	2014		x	x	x
Prednisolone	2006		x	?	
Topiramate	2007		x (neonatal seizures)	x	x

¹A) adrenal insufficiency; B) aphthous ulcers as occurring in colitis ulcerosa

Tab. 1 - Examples of active substances and related pediatric therapeutic need, priority status, studies needed (Source: TEDDY, Recommendation for Drug Development for Children, November 2015)

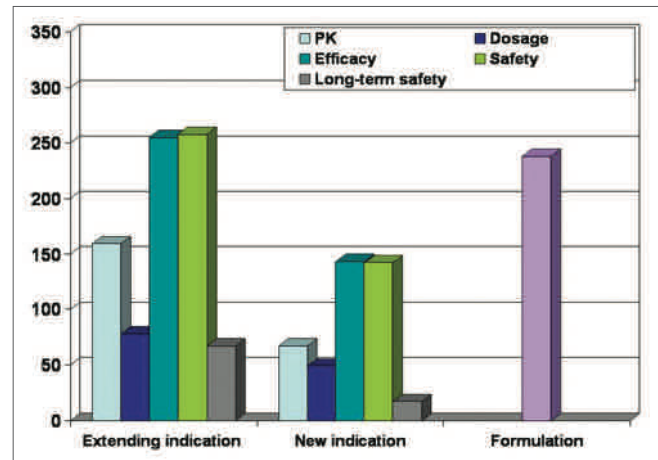


Fig. 1 - Type of study requested for the medicinal products included in the EMA Therapeutic Needs Lists (Source: TEDDY, Recommendation for Drug Development for Children, November 2015)

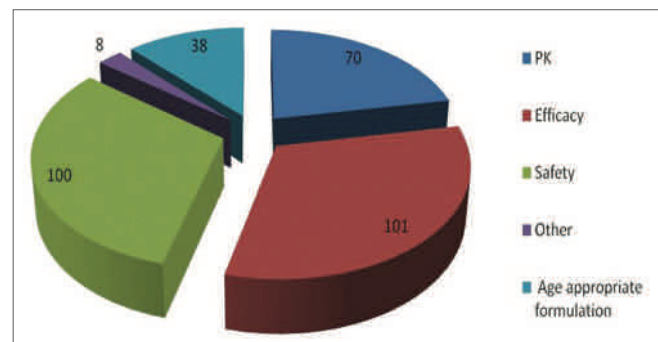


Fig. 2 - Specific needs in terms of study needed to develop the 135 active substances, as derived from Priority Lists (Source: TEDDY, Recommendation for Drug Development for Children, November 2015)

Both the lists, *Therapeutic needs list* and *Priority List*, include details on the existing formulations and on *the need* to identify a new formulation to cover the pediatric gap.

PDCCO set up at EMA, published and periodically updates these lists and for each substance indicates the need in term of studies to be performed in order to develop the pediatric indication and the appropriate pediatric form. Currently more than 400 active substances [8] have been identified in 15 therapeutic areas: anesthesiology, cardiovascular, diabetes (types I and II), endocrinology, gastroenterology, immunology, infectious diseases, nephro-urology, neurology, obstructive lung disease, oncology, ophthalmology, pain, psychiatry, rheumatology. About 1,500 studies are required on a total and 1/4 of this studies corresponds to a new pediatric formulation. In addition, 135 'off-patent' drugs are included in the 'Priority List'. Also for this group of drugs the total request in terms of studies is relevant and includes the provision of 70 new pediatric formulations. Moreover studies to develop 22 off-label drugs have been funded in 20 pediatric research projects by the European Commission [9] and in the context of these projects new age-appropriate formulations or dosage forms are under development. Of these ten are oral new formulations (six liquid, three tablets soluble or effervescent and one granule), seven new intravenous formulations and three intravenous dosage forms.

Tab. 1 provides some examples of active substances mentioned in the lists and the studies required by the PDCO whereas Figs. 1 and 2 show the number and the type of studies globally considered in the Therapeutic Needs and Priority Lists, respectively.

These lists do not mention the type of formulation that could result more appropriate to the specific pediatric use. However, many collaborative proposals are under discussion and this sector seems very promising in the next future both for academia and commercial sponsors. It should be also highlighted that recently the scientific community, and the public and private funding bodies as well, agree on the necessity to undertake a more precise selection of drugs of therapeutic interest to be developed for children. This selection is aimed at focusing scientific and human resources, as well as to assess the added market value for the sponsors of the future marketing authorizations.

Challenges and issues

The development of appropriate drug formulations for pediatrics still represents a challenge for the pharmaceutical industry. While in this paper only some key issues are discussed, for in-depth discussion on the topic the reader can refer to some recent excellent reviews [10-12].

A suitable formulation for each of the age groups must be optimized taking into account differences in the physiology and anatomy of pediatric populations, hence pharmacodynamics (PD) and pharmacokinetics (PK), as well as issues related to therapy acceptability and handling. Pediatric patients differ from adults and within age groups (i.e., newborns, infants, children, adolescents) with respect to drug action (receptor expression and function), greater regenerative potential and unique disease processes. From the PK point of view, determinants of the type of formulation for children are the differences in the age groups and ability to handle dosage forms. The design of formulations in pediatrics should carefully consider that patients with chronic diseases undergo growth and developmental changes during therapy. In addition, the disease/disorder being treated, genetic makeup and environmental influences must also be carefully considered.

Pediatric patients are dynamic with respect to drug disposition, due to developmental changes in body composition, drug metabolism and organ function.

For instance, infants (1 month-2 years) and children (2-11 years) may absorb, distribute, metabolize and eliminate (ADME parameters) pharmaceutical products with significant differences [13]. Moreover, particular toxicities in the active principle and excipients (see below) can be observed in infants and children. The ability to achieve target ADME parameters is critical. With reference to oral formulations, for example, age-related differences in ADME are very important to optimize drug efficacy and minimize toxicity. Among others, the following factors are worthy of special attention [14]:

- i) gastric pH and gastric emptying time during the neonatal period leading to variation in the absorption of many drugs;

Excipient	Use	Adverse effects
Aspartame	Sweetener (synthetic) in chewable tablets and liquid sugar-free formulations	As a source of phenylalanine, it can be harmful in pediatric patients affected by phenylketonuria; rare hypersensitivity reactions, cross-reactivity with sulfonamides
Benzalkonium chloride	Bactericidal preservative frequently found in beclomethasone and ipratropium bromide nebulizer solutions	Associated with bronchospasm in asthmatic children after inhalation; ocular toxicity in ophthalmic preparations
Benzyl alcohol	Solvent, preservative in several medicinal products and solutions, including dexamethasone, benzodiazepines (midazolam, lorazepam) and multivitamins	Due to accumulation of metabolites in blood and brain, toxicities include metabolic acidosis, neurotoxicity (seizures) and gasping syndrome
Ethanol	Solvent, preservative in oral liquid preparations (e.g. iron, ranitidine, phenobarbital)	CNS depressant; respiratory and cardiovascular adverse reactions at high concentrations
Lactose	Diluent in tablets, capsules, lyophilized powders, sweetener in liquid formulations, carrier in dry powders	Gastrointestinal symptoms and metabolic acidosis in lactose-intolerant subjects
Propylene glycol	Solvent with antimicrobial properties for oral and parenteral use (e.g., diphenhydramine, furosemide, prednisone, pseudoephedrine liquids, lorazepam injection)	High doses have been associated with hyperosmolarity causing laxative effects, metabolic acidosis, cardiovascular, hepatic and respiratory events, and neurotoxic effects in newborns and infants, with severe brain damage and life-long handicaps
Saccharin	Sweetener (synthetic) in both solid and liquid formulations	Cross-reactivity with sulfonamides; main adverse effects are dermatological (e.g., dermatitis, pruritus, photosensitivity) and systemic reactions (e.g., irritability, insomnia).
Sorbitol	Diluent in tablets, plasticizer for gelatin in capsules, vehicle and stabilizer in oral liquid formulations (e.g., diphenhydramine, ferrous sulphate, furosemide, prednisone, pseudoephedrine)	Osmotic diarrhea; contraindicated in pediatric patients with hereditary fructose intolerance and hypoglycemia
Sucrose	Sweetener in many pharmaceutical preparations (above all syrups)	Decrease in dental plaque pH, dissolving tooth enamel and promoting dental caries; contraindicated in pediatric patients with hereditary fructose intolerance and diabetes
Sulfites	Antioxidants	Possibly responsible for appearance of symptoms like dyspnoea and chest tightness in asthmatic children

Tab. 2 - Examples of excipients used in oral formulations, and related toxicity and safety risks in pediatric patients



- ii) differences in the apparent volume of distribution compared to adults and within the age groups of pediatric population;
- iii) slow total drug clearance in premature infants and neonates, due to immature hepatic and renal function;
- iv) under-expression of the hepatic microsomal enzymes, resulting in slower biotransformation of many drugs in premature infants and neonates;
- v) greater microsomal enzyme activity in prepubertal age, which requires higher mg/kg dosage to achieve suitable plasma levels of some drugs.

Besides PK/PD aspects, there are a number of important factors to be considered in developing pediatric drug formulations:

- i) palatability (i.e., good taste and texture) is a major determinant of oral formulations, chewable or dispersible preparations;
- ii) children are often unable to swallow capsules and tablets (until they are at least 6 years old), whereby the need of alternative options to the solid form;
- iii) drug solubility;
- iv) greater dose flexibility (drug dosing requires change as the child grows);
- v) small volumes of parenteral preparations to be administered with small needles [10]. The EMA guidelines suggest the following aspects to be taken into account in designing suitable formulations for pediatric use [15]:
 - the relevant developmental physiology of the patients in the target age group(s);
 - the condition to be treated and the characteristics of the child under pharmacological treatment (e.g., physical and mental disabilities, fluid restriction, co-medication, inability to swallow due to critical illnesses);
 - the critical dose (i.e., steep dose/PD response curve, narrow therapeutic range) and the dosing regimen (i.e., dose calculation, dose titration, dosing flexibility);
 - the age-associated activities of children in the target age group(s) (e.g., school, nursery);
 - the duration of the therapy and the dosing frequency;
 - the environment setting where the pharmaceutical product is likely to be used (e.g., hospital, community);
 - the characteristics and behaviors of the child and caregiver.

Historically, the inadequate appreciation of the developmental changes has led to many adverse outcomes. Examples include infant deaths from choking on albendazole tablets, lethal use of benzyl alcohol or diethylene glycol in sulfanilamide elixirs, electrolyte imbalance caused by high contents of sodium or potassium in parenteral formulations [16-18].

The oral route is the main route of administration in children for long-term treatments, whereas the parenteral route is the main route for neonates and emergency cases [10]. Oral dosage forms include liquid preparations (suspensions, solutions, syrups, drops, powder and granules for reconstitutions) and solid dosage forms (tablets, capsules, sprinklers, multiparticulates, orodispersible/chewable preparations). Parenteral forms includes intravenous, subcutaneous and intramuscular injections, and pump systems. Alternative nonoral routes of administration include rectal, dermal, nasal, pulmonary, and ocular routes. Recommended drug formulations for infants and children are oral solutions, oral suspensions, rapidly dissolving tablets, sprinkles/sachets, transcutaneous delivery systems, implantable reservoirs.

Oral formulations, albeit being pharmaceutical products of choice in pediatrics, have a noteworthy down side [11]. Solutions may contain potentially toxic excipients, whereas suspensions may often result in unequal delivery

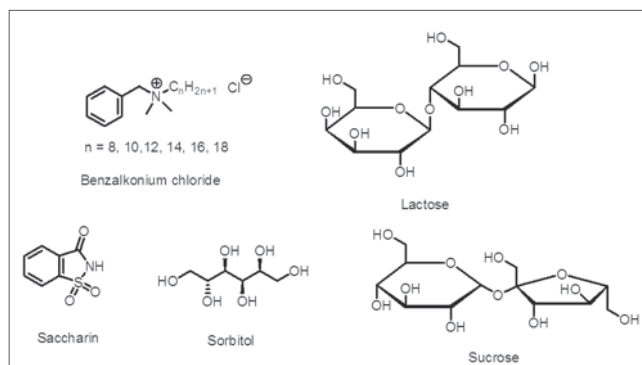


Fig. 3 - Structures of some excipients used in oral drug formulations whose main adverse effects in children are summarized in Tab. 1

over time or be affected by palatability limits, due to taste and consistency. In addition, liquid forms raise issues regarding stability (chemical, physical, or microbiological). Oral solids are associated with the risk of choking or chewing and with limited dose flexibility. Sprinklers and sachets may result in erratic absorption, whereas transcutaneous delivery systems much depend on uniform nature and composition of the coating.

The use of parenteral administration may be hampered by difficult application, local irritation, fluid overload, electrolyte imbalance, or poor drug acceptability. In neonates, intravenous administration may lead to volume overload, whereas measuring small dose volumes may cause large dosage variations and errors.

Focus on age-related toxicity of excipients

Excipients have been considered for a long time inert agents and their age-related toxicity largely underestimated [19, 20]. Excipients are used in almost all drugs as diluents, solvents, emulsifiers, glidants, disintegrants, sweeteners, preservatives, stabilizing, flavoring or coloring agents. They confer suitable shape, volume and consistency to the pharmaceutical preparation, allowing the drug to be easily administered and the active substance to be properly delivered to its site of action. A relevant source of information about the excipient-related toxicity and safety risks in pediatric drug formulations is the STEP database [21, 22]. Developed in collaboration by European Pediatric Formulation Initiative (EuPFI) and United States Pediatric Formulation Initiative (USPFI), the STEP database aims at improving systematic data collection on excipient toxicity and tolerance in children. STEP stands for 'Safety and Toxicity of Excipients for Pediatrics'. Accessible via EuPFI website, the STEP database holds general information, clinical and non-clinical data, *in vitro* data, regulatory references and reviews on the safety and toxicity of excipients. Major toxicity issues related to some excipients used in oral pediatric formulations are summarized in Tab. 2 (some structures in Fig. 3).

Aspartame, a synthetic sweetener used in some oral formulations, is a dipeptide of aspartic acid (Asp) and the methyl ester of phenylalanine (Phe). It is metabolized by three major pathways (Fig. 4) in the intestinal lumen and mucosal cells, releasing Asp (an excitotoxin), methanol (a neurotoxin) and Phe in the portal blood [23]. Aspartame, as a source of Phe in blood, should be totally avoided in children affected by phenylketonuria.

Benzyl alcohol (BA) is a solvent with antimicrobial properties. The BA-associated adverse reactions can include metabolic acidosis, CNS and respiratory toxic effects, which led the regulatory agencies to recommend

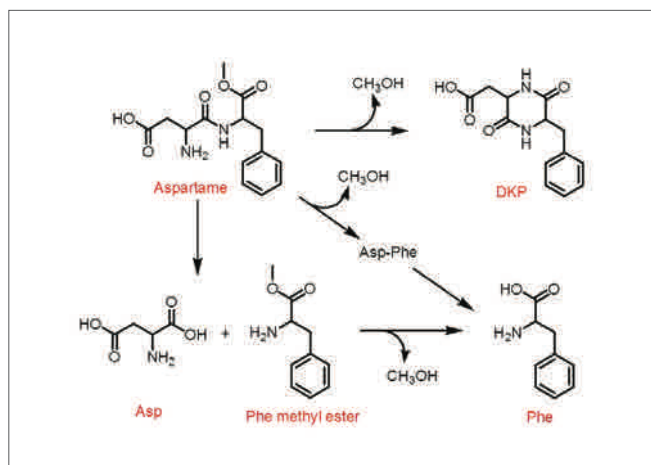


Fig. 4 - Metabolic pathways of the artificial sweetener aspartame. Asp: L-Aspartic acid; Phe: L-Phenylalanine; DKP: Diketopiperazine metabolite

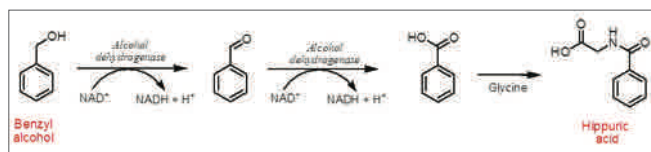


Fig. 5 - Metabolic pathway of benzyl alcohol in adults. The conversion of benzoic acid into hippuric acid decreases in neonates

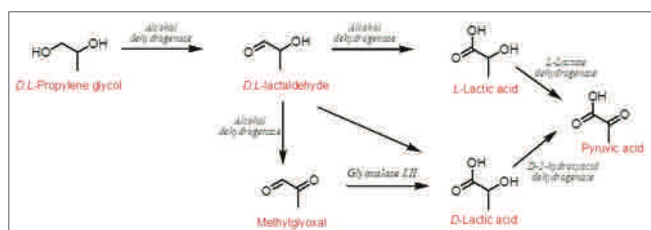


Fig. 6 - Metabolic transformation of propylene glycol into pyruvic acid

its exclusion from formulations for newborns [17, 18]. In adults, BA is metabolized to benzoic acid, followed by the conjugation with glycine to form hippuric acid (Fig. 5) which is excreted in the urine. The conjugation of benzoic acid with Gly is substantially decreased in neonates with rising toxicities [24-26].

Ethanol and propylene glycol (PG) are used as solvents in a variety of pharmaceutical products. Ethanol is rapidly absorbed from the gastrointestinal tract and metabolized to acetaldehyde, which is then oxidized to acetate. PK of ethanol in infants is not well understood. Ethanol is a CNS depressant and can cause respiratory and cardiovascular toxic effects at high concentrations [27, 28]. In OTC products, the maximum concentrations allowed are 0.5% v/v for children younger than 6 years, 5% v/v for 6-12 year of age and 10% v/v for adolescents (>12 years old). PG is metabolized to lactic and pyruvic acid (Fig. 6) and also excreted unchanged in the urine. In neonates PG is more accumulated ($t_{1/2}$ =16.9 h) than in adults ($t_{1/2}$ =5 h), thus provoking hyperosmolarity [29], CNS toxicities [30, 31] and other adverse effects. WHO established 25 mg/kg/day as an acceptable intake limit for adults. Acceptable limits in neonates are unknown. However, because of the serious toxicities, products with high levels of PG

must not administered in children <4 year and in pediatric dialysis patients. In Tab. 2 essential information is reported on adverse reactions of some other excipients in oral formulations for pediatric patients, such as the antimicrobial preservative benzalkonium chloride, the antioxidant sulfites, the artificial sweetener saccharin, and the natural sweeteners sucrose, sorbitol and lactose [11].

Cyclodextrins (CDs) are being investigated as excipients to help overcome drug delivery problems in pediatric medicine [32, 33]. CDs (Fig. 7) are cyclic oligosaccharides formed by a number of dextrose units of (α -1,4)-linked α -D-glucopyranose. They are characterized by a lipophilic central cavity and a hydrophilic outer surface. The parent CDs are made up of six (α -CD), seven (β -CD) or eight dextrose units (γ -CD). CDs, which have central cavities of different diameters, form inclusion complexes with hydrophobic drug molecules and can be used to improve the aqueous solubility of the drug. For β -CD, which itself has a relatively low aqueous solubility, substitution of the hydroxyl groups results in a marked improvement in the aqueous solubility of the derivative. Examples of β -CD derivatives are the sulfobutylether of β -CD (SBE- β -CD), the hydroxypropyl derivative of β -CD (HP- β -CD), and the randomly methylated β -CD (RM- β -CD).

Many drugs in the EMA priority list are hydrophobic (e.g., proton pump inhibitors, such as lansoprazole) or unstable (e.g., ganciclovir is stable in water for just 12 h at room temperature). CDs can actually help improving pediatric drug formulations, overcoming limitations of some drugs such as poor solubility and stability, and unpleasant taste [34]. CDs have indeed been used as complexing agents to increase the aqueous solubility of drugs poorly soluble in water, in order to improve their bioavailability and stability. In addition, CDs can be used to reduce or prevent gastrointestinal and ocular irritation, to reduce or eliminate unpleasant tastes, to provide better stability, to prevent drug-drug or drug-additive interactions within a formulation, or to convert oils and liquid drugs into microcrystalline or amorphous powders.

As regards toxicity and safety risks, although the oral availability of CDs is very low, high doses may cause reversible diarrhea and cecal enlargement

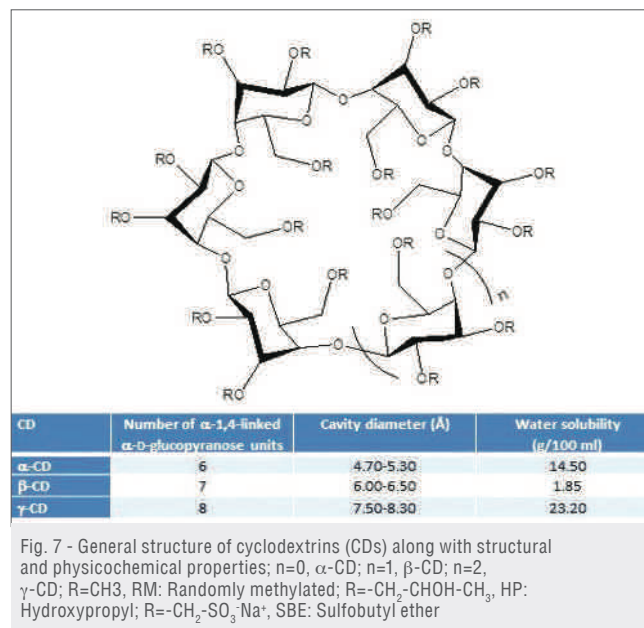


Fig. 7 - General structure of cyclodextrins (CDs) along with structural and physicochemical properties; n=0, α -CD; n=1, β -CD; n=2, γ -CD; R=CH₃, RM: Randomly methylated; R=-CH₂-CHOH-CH₃, HP: Hydroxypropyl; R=-CH₂-SO₃⁻Na⁺, SBE: Sulfobutyl ether



Administration route	α -CD	β -CD	γ -CD	RM- β -CD	HP- β -CD/ SBE- β -CD2
Oral					
PDE, mg/kg/day	120	¹⁰	200	N	160
TH adult	120	10	200	-	160
TH neonate	12	1	20	-	16
Parentera					
PDE, mg/kg/day	0.2	N	0.8	N	300
TH adult	0.2	-	0.8	-	300
TH neonate	0.02	-	0.08	-	10

¹Data taken from EMA, Background review for cyclodextrins used as excipients, November 20, 2014 (ref. [35]); N: No data for the respective route of administration
²Although different for their physicochemical properties, HP- β -CD and SBE- β -CD can be taken together from the toxicological viewpoint ulcerosa

Tab. 3 - Permitted Daily Exposures (PDEs) and suggested thresholds (THs) above which adverse reactions may occur in cyclodextrin (CD)-containing oral and parenteral pharmaceutical formulations¹

in animals, and to minimum extent in humans. Depending on the amount, CDs may influence the permeability of tissues and therefore the bioavailability of active substances given topically. In addition, CDs can cause nephrotoxic effects in animals at high systemic exposure, but there is no proof of these effects in humans so far. Data in children less than 2 years old are scarce. In Tab. 3 the Permitted Daily Exposures (PDEs) and suggested thresholds (THs), above which adverse effects may occur in CD-containing oral and parenteral pharmaceutical formulations. PDEs and THs are taken from the EMA draft report [35] are based on human data and, when not available, estimated on the basis of animal data.

Conclusions

The design and development of appropriate pharmaceutical formulations for the different age groups of pediatric patients still represents a challenge for pharmaceutical scientific community and industry. Neonates and infants below 6 months are the most vulnerable groups, because of the highest differences in drug action and ADME compared to adults. The EMA Therapeutic Needs List and the studies requested for optimizing appropriate formulations and dosage forms (Fig.s 1 and 2) indicate need and urgency to promote studies on child-appropriate formulations allowing better drug delivery, decrease of safety risks, including those related to excipients, and improved therapy compliance and dosage form handling. While many scientific proposals under discussion promise real advances in the sector, it appears important to improve public-private partnerships that progress in creating technological platforms for pharmaceutical pediatric formulations that support the applications to the pediatric pharmaceuticals of innovative technologies developed for adults (e.g., nanoparticle-targeted therapy, novel smart polymer-based drug delivery systems), while prioritizing unmet therapeutic formulation needs.

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Formulazioni farmaceutiche in pediatria: sfide e problematiche

Lo sviluppo di formulazioni farmaceutiche appropriate per i pazienti pediatrici rappresenta tuttora una sfida per la comunità scientifica e l'industria farmaceutica. È di tutta evidenza l'importanza di promuovere partenariati pubblico-privati che consentano di progredire nella creazione di piattaforme tecnologiche per lo sviluppo di formulazioni pediatriche in grado di ottimizzare il drug delivery e migliorare la sicurezza dei farmaci in età pediatrica, nel rispetto delle linee guida delle agenzie regolatorie.