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Daniel Bar-Shalom
Klaus Rose *Editors*

Pediatric Formulations

A Roadmap



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Chapter 24

Excipients and Active Pharmaceutical Ingredients

Parnali Chatterjee and Mohammed M. Alvi

Abstract Raw materials in pediatric formulations such as excipients, food ingredients, and active pharmaceutical ingredients (APIs) have received significant attention from regulatory agencies worldwide in recent times due to safety concerns. Not all excipients and food ingredients are “inert” and have been shown to interfere with the growth and development process in pediatric population. Though raw materials incorporated in drug products require extensive safety testing prior to their inclusion in the formulations, there are very few excipients that have undergone randomized clinical trial (RCT) in the pediatric subpopulation. Therefore, this chapter will provide an overview of selected excipients and APIs that are routinely included in pediatric products with reference to their chemical structure, chemical reactivity, and allowable daily intake for pediatric use.

Abbreviations

API	Active pharmaceutical ingredient
ADME	Absorption, distribution, metabolism, and excretion
FDA	US Food and Drug Administration
FDC	Food Drugs and Chemicals
GRAS	Generally recognized as safe
RCT	Randomized clinical trials

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24.1 Introduction

Excipients, ingredients in food products, and active pharmaceutical ingredients (APIs) in pediatric formulations have received significant attention from regulatory agencies worldwide due to safety concerns. Not all excipients are pharmacologically inactive and have been implicated in interfering with the growth and development process in pediatric population. Though raw materials incorporated in drug products require extensive safety testing according to the Federal Food, Drug and Cosmetic Act of 1938 prior to their inclusion in the formulations, there are very few excipients that have undergone randomized clinical trial (RCT) in pediatric subpopulation. Moreover due to the growth and developmental changes, there is huge variability in absorption, distribution, metabolism, and excretion (ADME) profile among the pediatric subpopulation, such that newborns and infants may be more sensitive to an excipient than a toddler. Hence, there are few excipients that can be considered “safe for consumption” within the pediatric subpopulation. This chapter will provide an overview of selected excipients and APIs that are routinely included in pediatric products with reference to their chemical structure, chemical reactivity, and allowable daily intake for pediatric use.

24.2 Excipients

Pharmaceutical excipients intended for incorporation into dosage forms are approved ingredients that are considered “inactive” and generally recognized as safe (GRAS) for human consumption. Excipients make up the bulk of any drug product and are included to impart stability, ensure accuracy and precision, homogenous blending, mask bitter taste, improve flowability, add bulk density, and control the release of API thereby improving patient compliance, bioavailability, efficacy, and reduce toxicity of the API [1, 2]. Though excipients are considered “inactive” and can be exempted from listing on certain drug products, they are required by the FDC Act to be listed on ophthalmic, topical, and parenteral products. Hence, excipients are subjected to exhaustive short-term and long-term toxicological studies prior to their inclusion in drug products for adult population but are not tested in pediatric subpopulation. Studies in pediatric population are a challenge from an ethical stand-point and are limited by blood sample availability and physiological changes that occur early in life and up to adulthood [3]. Moreover, information from clinical studies establishing efficacy and dosage regimen for adult population cannot be extrapolated to the pediatric population due to the rapid growth and developmental changes occurring in children. Currently, pediatric medications are available as drops, elixirs, syrups, suspensions, sprinkles, capsules, orally disintegrating tablets, chewable tablets, injectables, etc. [4]. Many excipients such as lactose and sorbitol when included in pediatric formulations can induce diarrhea in children, benzyl alcohol can cause toxicity in neonates, while aspartame-based sweeteners can induce seizures and headaches in children,

adverse effects that are not commonly observed in formulations for adult population. Therefore, the objective of this section is to highlight the excipients commonly found in pediatric products, chemical reactivity of the functional groups present in the molecules, impurities present in the excipients, and concentrations at which excipients exert their toxicity in pediatric population.

24.2.1 Classification of Excipients

Excipients can be classified depending on the (1) origin of source such as plant, animal, mineral, and synthetic-based, (2) functional role they play in the formulation such as binders, diluents, disintegrants, fillers or bulking agents, glidants, lubricants, coloring agents, preservatives, sweeteners, surfactants, solvents, coating agents [5], and (3) chemical substituents present in the excipients such as alcohols, acids, esters, carbohydrates, glycerides, halogenated derivatives, mercury salts, sulfites, etc. Notable examples of excipients found in pediatric formulations are included in Table 24.1.

Table 24.1 Classification of pharmaceutical excipients

1. Classification of pharmaceutical excipients based on function
Binders
<i>Example:</i> PVP, HPMC
Coloring agents
<i>Example:</i> E number colorants
Coating agents
<i>Example:</i> Phthalates
Diluents
<i>Example:</i> Lactose, microcrystalline cellulose
Disintegrants
<i>Example:</i> Sodium starch glycolate, croscarmellose sodium
Fillers/bulking agents
<i>Example:</i> Lactose
Glidants
<i>Example:</i> Colloidal SiO ₂
Lubricants
<i>Example:</i> Magnesium stearate, sodium stearyl fumarate, sodium behenate
Preservatives
<i>Example:</i> Sodium benzoate, thiomerosal
Sweeteners
<i>Example:</i> Sorbitol, mannitol, dextrose, aspartame, saccharin, sucralose
Surfactants
<i>Example:</i> Tweens, spans, polysorbates, poloxamers, lecithins
Solvents
<i>Example:</i> Ethyl alcohol, benzyl alcohol, propylene glycol, sorbitol, PEGs

(continued)

Table 24.1 (continued)

2. Classification of pharmaceutical excipients based on origin of source
Animal source
<i>Example:</i> Lactose, gelatin, stearic acid
Mineral origin
<i>Example:</i> Silica, calcium phosphate
Plant source
<i>Example:</i> Alginates, starches, sugars, cellulose
Synthetic excipients
<i>Example:</i> Polyethylene glycol, polysorbates, polyvinylpyrrolidone
3. Classification of pharmaceutical excipients based on chemical substituents
Alcohols
<i>Example:</i> Ethyl alcohol, benzyl alcohol, propylene glycol
Carboxylic acids
<i>Example:</i> Benzoic acid
Carbohydrates
<i>Example:</i> Mono-, di- and polysaccharides, sucrose, lactose, mannitol
Dyes
<i>Example:</i> Tartrazine, amaranth
Esters/ethers
<i>Example:</i> Fatty acid esters or ethers
Glycerides and waxes
<i>Example:</i> Peanut oil, bees wax
Halogenated hydrocarbon derivatives
<i>Example:</i> Freons, chlorbutol, halothane
Organic mercurial salts
<i>Example:</i> Thiomerosal
Phenolic compounds
<i>Example:</i> BHA, BHT
Proteins
<i>Example:</i> Albumin, gelatin
Polymers
<i>Example:</i> HPMC, Eudragits

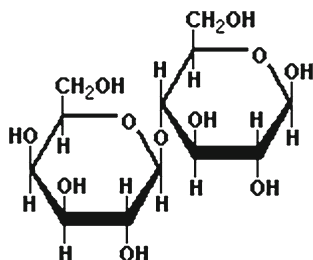
24.2.2 *Properties of Selected Excipients*

No excipient is inert and above a certain concentration can produce adverse reactions in the pediatric population. Based on the FDA Guidance document of 2005, excipients for pediatric formulations should be chosen such that the ADME profile of the target population, length of the therapy, and dosing interval is taken into consideration. In addition, substitutions to the commonly used excipients in pediatric formulations can be made that include reducing the amount or elimination of preservatives such as thimerosal, benzyl alcohol, and propylene glycol from vaccines and other drug products that are administered to children below the age of 6 years. In a number of vaccines and formulations, thimerosal, benzyl alcohol, or propylene glycol has been replaced by benzalkonium chloride, methyl and propylparaben (0.1–0.3 %), bronopol

(2-bromo-2-nitropropane-1,3-diol), sodium azide, or 2-phenoxyethanol. Salient properties of excipients commonly found in pediatric formulations are described in the following section and allowable daily intake is given in Table 24.2.

24.2.2.1 Fillers/Binders

Lactose



Synonyms: Lactin; Lactose; D-Lactose; Galactinum; Aletobiose; Osmolactan; Lactobiose; Milk sugar

General appearance: White powder, either in crystalline or amorphous state

Molecular formula: C₁₂H₂₂O₁₁

Formula weight: 342.3 g/mole

Water solubility: Very soluble in water (5–10 g/100 mL)

Lactose is a reducing disaccharide of glucose and galactose. It can occur in two anomeric forms, α-lactose (monohydrate) and β-lactose (anhydrous). The two forms can be used as a diluent and filler for direct compression and wet granulation in tablets and capsules, and a bulking agent for powders in 20 % of all formulations in the market. In crystalline form it is less reactive, while the carbonyl group in amorphous lactose can react readily with primary and secondary amines in the API via Maillard reaction to give a Schiff's product, which can undergo Amadori rearrangement and form Glycosamine [6]. Maillard reaction is known to occur in infants due to carbohydrate-derived carbonyl groups present in milk-based infant formulas and protein amino groups [7]. The by-products of Maillard reaction can function as electrophiles and cause adverse reactions in newborns and infants. Such reaction products have been shown to cause histological changes in the proximal tubules of kidneys in rats and increased levels of microprotein in human urine [8, 9].

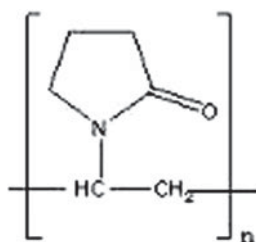
Lactose is absorbed from the gastrointestinal tract (git) once it is hydrolyzed by the enzyme “lactase” into glucose and galactose. Hence, children deficient in “lactase,” are unable to absorb lactose (due to congenital defect or lack of the enzyme) and develop flatulence, diarrhea, gastrointestinal bloating following ingestion of milk due to the build-up of lactic acid, hydrogen, and carbon dioxide. Lactose intolerance in infants and children can lead to prolonged episodes of bloating, diarrhea, dehydration, and metabolic acidosis [9]. Adverse effects due to lactose intolerance can develop in infants and children with ingestion of less than 3 g of lactose.

Table 24.2 Allowable daily intake (ADI) in children, no observable adverse event level (NOAEL), adverse effects of pharmaceutical excipients in the formulations [23, 24]

Excipient	Allowable daily intake (ADI)	Adverse effects
<i>Diluent</i>		
Microcrystalline cellulose	Not specified	Intestinal absorption, long-term effect not known, should not be used in children <2 years
<i>Dyes</i>		
“E number” additives: Sunset yellow (E110), Quinoline yellow (E104), Carmoisine (E122), Allura red (E129), Tartrazine (E102), and Ponceau 4R (E124)	2.5 mg/kg (Sunset yellow)	Negative effect on children’s behavior and ADHD
<i>Solvents/co-solvents</i>		
Benzyl alcohol (BA)	Not specified	Toxic syndrome observed in neonates (attributed to the practice of “flushing out” umbilical catheters with solutions containing BA); severe respiratory complications and even death in neonates caused by dilution of nebulization solutions with BA-preserved saline
Ethyl alcohol	Max 10 % (12 years) Max 5 % (6–12 years) Max 0.5 % (<6 years)	Due to high blood–brain barrier permeability; CNS effects at 0.01 g/L; intoxication, lethargy, stupor, coma, respiratory depression, cardiovascular collapse
Peanut oil	Not specified	Use in infant formula and topical preparations can lead to later episodes of hypersensitivity
Propylene glycol	25 mg/kg	No known toxic dose; but potentially life-threatening complications such as cardiovascular, hepatic, respiratory, and CNS adverse reactions especially in neonates where the biological half-life is prolonged to 17 h compared with adults, 5 h
<i>Sweeteners</i>		
Aspartame	40 mg/kg/day	Source of phenylalanine, can cause phenylketonuria; hyperactivity in children but unproven
Lactose	Not specified	Diarrhea, gaseousness or cramping; intestinal disorders
Saccharin	5 mg/kg/day	Hypersensitivity reactions (mainly dermatologic); pediatric with allergy to sulfonamides should avoid saccharin; carcinogenic potential (banned in Canada)
Sorbitol	0.3 g/kg	Diarrhea, gastrointestinal disorder
Sucralose	5 mg/kg/day	Not specified
<i>Surfactant</i>		
Polysorbate 80	10 mg/kg/day	E-Ferol syndrome (Thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) in low birthweight infants
Polyvinylpyrrolidone	0–50 mg/kg	Not specified
<i>Preservatives</i>		
Benzoic acid, Potassium benzoate, Sodium benzoate	up to 5 mg/kg (sum of all)	Caffeine and sodium benzoate should be injected simultaneously; elicits non-immunological contact reactions including urticaria and atopic dermatitis in neonates
Thimerosal	Not specified	Possible links with toxicity in pediatric vaccines and childhood autism; though unproven

Therefore, in pediatric formulations, lactose can be substituted with starch, calcium hydrogen phosphate dehydrate, erythritol, and powdered cellulose. These powders have flow properties similar to lactose (calcium hydrogen phosphate dehydrate has a smaller angle of repose than lactose), and produce tablets that can disintegrate in shorter time than lactose.

Polyvinylpyrrolidone



Synonyms: PVP, polyvidone povidone, poly [1-(2-oxo-1-pyrrolidinyl)ethylen] 1-ethenyl-2-pyrrolidon homopolymer 1-vinyl-2-pyrrolidinon-polymer copovidone

General appearance: White powder

Molecular formula: (C₆H₉NO)_n

Formula weight: Average MW 360,000 g/mole

Water solubility: Readily soluble

PVP can be used as a binder, clarifying agent, stabilizer, bodying agent, tableting adjunct, dispersing agent, and for masking taste in formulations. Polyvinylpyrrolidone-based excipients including Povidone and Crospovidone may contain peroxides, formates, and aldehydes as by-products that can be generated as a result of the manufacturing processes or due to oxidative instability of the excipients over time and are more reactive than hydrogen peroxide [10]. Recently, PVP has been shown to cause immediate or contact dermatitis reaction in children [11].

Hydroxypropylmethylcellulose



Synonyms: Modified cellulose; propylene glycol ether of methyl cellulose

General appearance: White or slightly beige powder or granule

Molecular formula: C₃H₇O

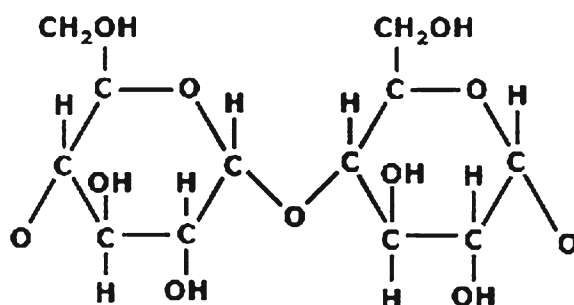
Molecular weight: 59.09 g/mole

Water solubility: Soluble

Hydroxypropylmethylcellulose (HPMC) is used as a thickener for aqueous and non-aqueous systems that can produce clear films with grease resistance, can function as binders, lubricants, steric stabilizer and aids in water retention. Inclusion of

HPMC and HPMCAS (hydroxypropylmethylcellulose acetate succinate) as a coating agent in oral formulations can lead to the formation of minor quantities of glyoxal or dialdehyde (phthalamide and succinamide impurities) impurities with certain APIs such as duloxetine hydrochloride [12] and cause toxicity. Formation of the impurities is hastened in the presence of moisture and high temperature. Since duloxetine is prescribed to the pediatric population for treating anxiety disorders, levels of the impurities are closely monitored during formulation development.

Starch



Synonyms: Alpha-starch, (2*R*,3*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-6-[(2*R*,3*S*,4*R*,5*R*,6*S*)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3-yl]oxy-oxane-3,4,5-triol

General appearance: Fine, white, odorless powder.

Molecular formula: (C₆H₁₀O₅)_n

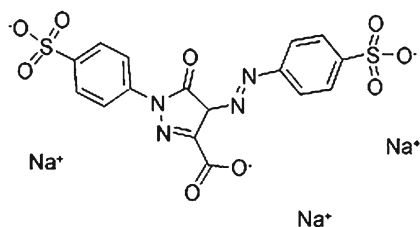
Molecular weight: Variable hydrophilic polymer

Water solubility: Very soluble

Starch can be used as a binder for wet granulation, disintegrating agent, diluent in capsules, and powder formulations. Lignin, maltose, and hemicellulose are known impurities in starch. Maltose and acetyl formoin, impurities found in starch, have been implicated in the formation of Amadori rearrangement degradation products with APIs containing primary and secondary amines such as antiallergic medication, desloratadine [13]. Since starch is an excipient that is routinely found in most solid dosage forms, studies involving interactions between starch and APIs are especially warranted before inclusion in pediatric formulations.

24.2.2.2 Coloring Agents

Tartrazine



Synonyms: CI NO 19140; CI acid yellow 23; CI 19140; E102; Lake tartrazine; Kiton Yellow T; Hydrazine yellow; Food yellow No. 4

General appearance: Deep yellow powder

Molecular formula: $C_{16}H_9N_4Na_3O_9S_2$

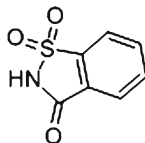
Molecular weight: 534.36 g/mole

Water solubility: Very soluble

Azo dyes such as tartrazine, amaranth, Erythrocin B, ponceau, indigo carmine improve aesthetics of a product by imparting color to the formulation but are known to produce adverse effects such as contact dermatitis, gastrointestinal intolerance, bronchospasm, eosinophilia, angioedema, and urticaria in children. These side effects observed with azo dyes are similar to those observed with aspirin. Moreover, clinical trials have implicated azo dyes to hyperactivity in children, but recent controlled and RCT with azo dyes have refuted the claim [14]. Such dyes can be substituted with vegetable dyes such as annatto, malt beta-carotene, and turmeric or not used at all in pediatric formulations.

24.2.2.3 Sweeteners

Saccharin



Synonyms: Saccharin; Saccharin 550X; Syncal[®], *o*-benzoic acid sulfimide

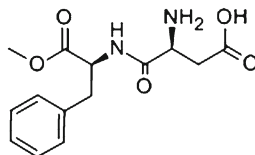
General appearance: White crystals, odorless or faintly aromatic odor, sweet in taste.

Molecular formula: $C_7H_5NO_3S$

Molecular weight: 183.18 g/mole

Saccharin is considered a low calorie-artificial or non-nutritive sweetener according to the Academy of Nutrition and Dietetics [15]. Non-nutritive sweeteners such as saccharin have no carbohydrate value and hence produce minimal or no energy. Daily intake of saccharin has been found to be 0.2–0.9 mg/kg in adult population, while that number is 3-times in diabetics. In children, amount of saccharin that is ingested through chewable acetaminophen or aspirin tablets has been found to be similar to that found in diet soda cans and considered to be “excessive” by an FDA/NCI sponsored epidemiology study. Saccharin is an *o*-toluene sulfonamide that causes “sulfa” type of hypersensitivity reaction in children including wheezing, urticaria, pruritis, nausea, vomiting, diarrhea, tachycardia, headache, diuresis and sensory neuropathy [14]. Infant formula sweetened with saccharin has been found to induce insomnia, irritability, and hypertonia. Therefore, American Medical Association recommends limited intake of saccharin in infants and pregnant woman.

Aspartame



Synonyms: L-aspartyl-L-phenylalaninemethyl ester; L-asp-phemethylester; *H*-asp-pheome; Equal; Aspartame

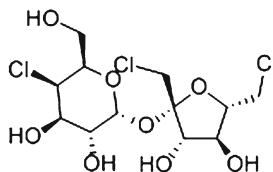
General appearance: White powder or tablets

Molecular formula: $C_{14}H_{18}N_2O_5$

Molecular weight: 294.3 g/mole

Similar to saccharin, aspartame is a non-nutritive sweetener with minimal or no carbohydrate value and regarded as safe by the FDA [15]. It is an aspartic acid and phenylalanine derivative that is increasingly used in sugar-free and chewable formulations. Serum levels of phenylalanine can significantly increase on ingestion of high amounts of aspartame. Hence, content of phenylalanine should be clearly indicated in the drug product label. Consumption of aspartame should be closely monitored, especially in children with autosomal recessive phenylketonuria, since levels of phenylalanine could significantly rise on ingestion of aspartame. Daily intake of aspartame in children can be between 5 and 10 mg/kg, for those without any dietary restrictions. A number of adverse effects such as headaches, panic disorders, mood changes, and seizures have been reported as a result of high dose (>30 mg/kg/day) and long-term ingestion of aspartame, but none of adverse effects could be proven by a single-dose randomized double-blind clinical trial [16]. Aspartame can be replaced by stevia, date sugar, maple sugar, maple syrup molasses, and agave nectar in pediatric formulations.

Sucralose



Synonyms: 1,6-dichloro-1,6-dideoxy-beta-D-fructofuranosyl 4-chloro-4-deoxy-alpha-D-gala; 4,1',6'-trichloro-4,1',6'-trideoxy-galacto-sucrose

General appearance: Off-white amorphous solid

Molecular formula: $C_{12}H_{19}Cl_3O_8$

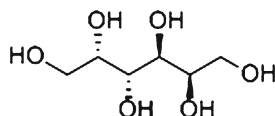
Molecular weight: 397.63 g/mole

Water Solubility: Soluble

Sucralose is a non-nutritive sweetener that is regarded as safe by the FDA. It is a chlorine derivative of sucrose and is 600 times as sweet as sucrose. It finds its

application in the pediatric formulations, food and beverages [17]. Sucralose is slowly absorbed from the gastrointestinal tract and has a greater impact on the gut bacteria. Recent data suggest a link between increased intake of saccharin and sucralose to the prevalence of irritable bowel syndrome in children and in adult population [18].

Sorbitol



Synonyms: Cholaxine; Diakarmon; D-Sorbit; D-Sorbite

General appearance: White crystalline powder, odorless colorless solid, sinks and mixes with water

Molecular formula: $C_6H_{14}O_6$

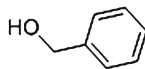
Molecular weight: 182.17 g/mole

Water solubility: Soluble

Sorbitol is a hexahydric polyol and a nutritive sweetener which produces sweetness with less energy intake (2.6 vs 4 kcal/g of energy for sucrose). Polyols are labeled as “sugar-free” by the Academy of Nutrition and Dietetics [15]. Ingestion of sorbitol at doses of 0.5 g/kg body weight has been shown to cause gastrointestinal distress, bloating, diarrhea, and abdominal pain in children depending on the age due to the metabolism of sorbitol to pyruvic acid and lactic acid by the liver. At higher doses (10–20 mg/kg body weight), sorbitol can produce a laxative effect in the intestine, shortens the transit time, thereby decreases energy value. Since newborns and infants have immature and developing epithelial barriers and drug metabolizing enzymes, absorption of sorbitol is limited, but enhanced in the presence of glucose and fatty acids. Accumulation of sorbitol in the body of newborns and infants has been implicated in diabetic-like symptoms in the body such as retinopathy. Therefore, pediatric formulations containing sorbitol have labeling requirements that state the content of sorbitol in the drug product.

24.2.2.4 Alcohols

Benzyl Alcohol



Synonyms: (Hydroxymethyl) benzene; Bentalol; Benzalalcohol; Benzalcohol; Benzenemethanol;

General appearance: A clear colorless liquid with a pleasant odor, slightly denser than water, flash point 194 °F, boiling point 401 °F, contact may irritate skin, eyes, and mucous membranes.

Water solubility: Very soluble

Synonyms: Benzotron(r); benzoic acid sodium salt; Fema 3025

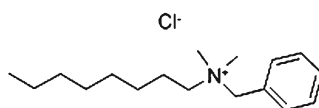
Molecular formula: $C_7H_5NaO_2$

Molecular weight: 144.1 g/mole

Water solubility: Soluble

Sodium benzoate is used as a preservative in pediatric formulations containing amoxicillin-clavulanic acid and other antibiotics. It is regarded as safe by the FDA. In some cases, sodium benzoate has been implicated in cutaneous urticaria in children through non-immunologic pathways [21].

Benzalkonium Chloride



Synonyms: Benzyldimethylalkylammonium chloride; BKC; alkyl (C 14–16) dimethylbenzyl-ammoniumchlorides; benzyldimethyl (mixedalkyl) ammoniumchloride

General appearance: Colorless or yellowish powder or gummy amber solid, aromatic odor, very bitter taste

Molecular formula: $C_{17}H_{30}ClN$

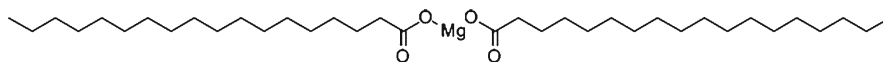
Molecular weight: 283.88 g/mole

Water solubility: Soluble

Benzalkonium chloride is used as a preservative, biocide, surfactant, emulsifying agent, and as a pigment dispersant. Children are exposed to benzalkonium chloride through nasal sprays containing corticosteroids, decongestants, and saline solution [19]. Benzalkonium chloride produces bronchoconstriction, cough, pruritis, facial flushing, and burning sensation in a dose-dependent manner. Since the concentration of benzalkonium chloride in nasal products for children from a multi-dose bronchodilator (50 μ g/0.5 mL) is low, children are mostly likely not susceptible to the adverse effects of the preservative. In addition, single-dose vials of bronchodilators can be recommended for children without the need for preservation using benzalkonium chloride.

24.2.2.6 Lubricants

Magnesium Stearate



Synonyms: dibasic magnesium stearate; Dolomol; magnesium di-stearate; Magnesium stearate medicinal; stearate de magnesium; magnesium octadecanoate

General appearance: White powder

Molecular formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.24 g/mole

Water solubility: Insoluble

Magnesium stearate is used as a diluent and an anti-adherent agent in formulations. It is a mixture of magnesium salt of fatty acids, palmitic acid and stearic acid. Magnesium stearate and stearate salts can interact with APIs, especially drugs that are prone to hydrolysis via ion-catalyzed mechanism such as aspirin, leading to degradation products such as salicylic acid, salicyl salicylic acid, and acetyl salicyl salicylic acid [12]. A casual link between aspirin related drugs and Reye's syndrome, which is characterized by hypoglycemia, hypoketonemia, elevated ammonia, and organic aciduria in pediatric population, has long been established in formulations containing magnesium stearate and aspirin [22]. Fatty acids in magnesium stearate are susceptible to contact dermatitis, though rare cases of allergies have been noted in children. Despite numerous reports of incompatibilities magnesium stearate continues to be a widely used lubricant in oral dosage forms.

24.3 Conclusions

Excipients serve many functions in a formulation by improving product delivery, as an absorption enhancer and improve flow properties of an API during manufacturing process. Therefore, there are very few drug products that can be manufactured without an excipient. Excipients incorporated in pediatric formulations require safety evaluation in specific subset of the pediatric population due to the variability in ADME profile among the subpopulation. RCT to evaluate the safety of excipients in pediatric population are not only limited by availability of pediatric patients but by blood samples and difficulty in extrapolating the results to the pediatric subpopulation. It is highly unlikely that all excipients would be subjected to RCT in pediatric population such that the recommended daily intake could be determined, nor will there be a list of "selected excipients" that could be exclusively used in pediatric population. It would therefore be in the best interest of the scientific community to evaluate the safety profile of the excipients included in the drug products during the course of the drug development process in the pediatric population.

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