Pharmaceutical excipients and pediatric formulations

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INTRODUCTION

Dosage formulations developed specifically for pediatric population have been few and far between due to the fact that children require fewer medications to treat their ailments unlike adults. Hence, the impetus to develop dosage forms for pediatric population has been slow. Almost all therapeutic agents administered to pediatric population are adult dosage forms that lack any labelling information for dosing in pediatric population, suffer from patient compliance, are administered at doses not appropriate for pediatric population and contain many formulation excipients have been shown to produce toxicity in pediatric population [1]. Some of the most common toxicities encountered with excipients in pediatric population include bronchospasms due to the presence of benzalkonium chloride in antihistaminic drugs, headaches and seizures as a result of aspartame which is used as a sweetener, and the use of benzyl alcohol which caused toxicity in neonates, hyperosmolality and lactic acidosis due to propylene glycol [2, 3]. It is only recently that drugs marketed in the US are being clinically evaluated in pediatric population [4] though the short-term and long-term effects in children of most excipients used in these formulations are not yet fully known. Pharmaceutical excipients in dosage forms have long been considered as inert additives that serve multiple functions by imparting stability to the active pharmaceutical ingredient (API), ensures accuracy and precision of dosing API, ensures patient compliance by improving the taste of bitter API, improves flowability of API through the hopper and adds bulk density to the API during the processing of dosage forms, can be incorporated to control the release of API thereby improving the bioavailability, efficacy, and toxicity of the API (2, 3). Most excipients intended for adult use are approved excipients that are generally recognized as safe (GRAS) for human consumption. These excipients have undergone exhaustive short-term and long-term studies for toxicological endpoints in adult population but not in pediatric sub-population. Studies in pediatric population are a challenge from ethical stand-point, limited blood sample availability, and physiological changes that occur during the early life up to adulthood. Due to the rapid growth and developmental changes children cannot be considered as small adults (Table 1). Therefore, the objective of this paper is to highlight the safety concerns of the excipients based on their chemical structure, chemical reactivity of the functional groups present in the molecules, and doses at which the excipients exert their toxicity in pediatric population. The paper will also discuss substitutions that can be made for excipients known to elicit safety issues in pediatric population.

KEYWORDS
Exipients; pediatric formulations; allowable daily intake; adverse reactions; absorption; distribution; metabolism; excretion.

ABSTRACT
Pharmaceutical excipients used in pediatric formulations have received significant attention from regulatory agencies worldwide due to the safety concerns. Many excipients have been implicated in interfering with the growth and development process of pediatric population. Excipients require thorough short-term and long-term safety evaluation in pediatric population prior to their incorporation in pediatric formulations. This mini-review will discuss the safety impact of the excipients with reference to the chemical structure, chemical reactivity, and doses used, to the toxicity observed in pediatric population. In addition, the review will highlight the excipients that can be substituted for in pediatric formulations to ensure safety and efficacy of such products.

REGULATORY GUIDELINES AND PEDIATRIC FORMULATIONS
Development of formulations for pediatric population is challenging since regulatory guidelines that govern the development of dosage forms for pediatric consumption have not been fully implemented worldwide. The International Pharmaceuticals Excipients Council (IPEC), the European Medicines Agency (EMA), and Centre for Drug Evaluation Research (CDER) of the US Food and Drugs Administration (FDA) have provided guidelines for conducting preclinical studies for the safety evaluation of pharmaceutical excipients in 1997, 2003 and 2005, respectively [4]. These guidelines provide framework for short-term and long-term safety testing of excipients for adult consumption. Though there are provisions for reproductive testing of the excipients, none of the guidelines recommend the conduct of ADME studies over the entire pediatric age group for which the drugs and the excipients will be used. Recently, CDER has solicited comments on a guidance document titled ‘Limiting the use of certain phthalates as excipients in CDER-regulated products’ in March 2012. The guidance document calls for limiting the use of phthalates such as, dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) that are commonly used as plasticizers in enteric-coating agents of solid oral dosage forms to maintain flexibility, due to their potential to produce developmental and reproductive toxicity in laboratory studies.
animals. Formulations developed for pediatric use need to meet certain criteria including development of appropriate route of administration that would be compliant with pediatric age group; orally dissolving; tasteless; show adequate light, humidity, and heat stability; amenable to dose titration such that they can be dispersed to pediatric population from pre-term new-born infants (<37 weeks of gestation) to adolescents (12-18 years), and have suitable drug release patterns (3, 4). Excipients used in developing such formulations for pediatric consumption therefore must meet certain safety criteria. The next section will highlight some of the excipients found in marketed formulations with reference to the chemical class, chemical structures, and functional use of the excipients in the formulation.

CLASSIFICATION OF EXCIPIENTS

Excipients are broadly classified based on the role they play in the formulation (5) as:

a) Binders (PVP, HPMC)

b) Colouring agents (E number colorants)

c) Coating agents (phthalates)

d) Diluents (lactose, microcrystalline cellulose)

e) Disintegrants (sodium starch glycolate, croscarmellose sodium)

f) Fillers/bulking agents (lactose)

g) Glidants (colloidal SiO2)

h) Lubricants (magnesium stearate, sodium stearyl fumarate, sodium benenate)

i) Preservatives (sodium benzoate, thimerosal)

j) Sweeteners (sorbitol, mannitol, dextrose, aspartame, saccharin, sucralose)

k) Surfactants (Tweens, spans, polysorbates, poloxamers, lecithins)

l) Solvents (ethyl alcohol, benzyl alcohol, propylene glycol, sorbitol, PEGs).

They can be further classified based on their origin or source, such as:

a) Animal source (lactose, gelatin, stearic acid, etc.)

b) Mineral origin (silica, calcium phosphate, etc.)

c) Plant source (algates, starches, sugars, cellulose, etc.)

d) Synthetic excipients (polyethylene glycol, polysorbates, polyvinylpyrrolidone, etc.).

Another type of classification is based upon the chemical class of excipients (1) that include:

a) Alcohols (ethyl alcohol, benzyl alcohol, propylene glycol),

b) Carboxylic acids (benzoic acid)

c) Carbohydrates (mono-, di-, and polysaccharides) (sucrose, lactose, mannitol)

d) Dyes (tartrazine, amaranth)

e) Esters / ethers (fatty acid esters or ethers)

f) Glycerides and waxes (peanut oil, bees wax)

g) Halogenated hydrocarbon derivatives (freons, chlorbutol, halothane)

h) Organic mercurial salts (thimerosal)

i) Phenolic compounds (BHA, BHT)

j) Proteins (albumin, gelatin)

k) Polymers (HPMC, Eudragits)

Table 1. Chemical classification, structures of excipients, and functional use of pharmaceutical excipients in the formulations.
The chemical classes of excipients, structures of excipients representative of the chemical class and their functional attributes are listed in Table 1.

**ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)**

Absorption, distribution, metabolism, and excretion (ADME) profile in the pediatric sub-population undergoes substantial changes during the first years of life (Table 2) such that significant variability in the pharmacokinetics (PK) of the identical dosage form is observed in pediatric population as compared to that in the adult population. Growth and developmental changes that alter ADME parameters can lead to changes in the clearance, volume of distribution, mean residence time (MRT) of the drug and metabolites in the body and ultimately the exposure to the drug (area under the curve, AUC), which are important PK parameters (6).

**Absorption**

Drugs are mostly absorbed from the small intestine, but due to the immaturity of tissues in pediatric population, there are significant variations in the absorption of drugs (6.7). The gastric acid output of the stomach reaches maturity and approaches adult levels only by 3 months of age. The gastrointestinal motility is significantly delayed in neonates and reaches maturity by 6-8 months of age. Gastrointestinal flora is underdeveloped in neonates and infants contributing to significantly higher absorption of drugs and therefore increased susceptibility to toxic drugs and metabolites as seen with penicillins that show higher absorption in infants. The gastrointestinal flora reaches adult levels by the first year of life.

There are other physiological changes that can contribute to significant absorption of drugs in pediatric population such as immature epithelial barrier as well as epidermal barrier leading to increased absorption of drugs (7,8). Increased hydration of skin and surface area of skin to weight ratio adds to increased percutaneous absorption of drugs in neonates. Drug transporters that play an important role in the uptake and efflux of drugs into and from the cells of different tissues such as intestines, liver, kidney, and others, show differential expression in the pediatric population, as the organs go through the growth and development processes. It has been shown that new-borns have low rate of renal excretion than children and adults, while toddlers require a higher dose per kg body weight compared to adults.

**Distribution**

Similarly, distribution of drugs can be severely impacted in pediatric sub-population as the amount of body water is significantly higher in neonates (85 percent) as compared to the adults (55 percent). Therefore, drugs that have a propensity to partition into aqueous layers are highly distributed (Volume of distribution or Vd) in neonates as compared to adults. The Vd of lipophilic drugs varies in the pediatric population as compared to the adults. Total body fat increases in children between 5-10 years followed by a decline through adolescents. In addition, plasma protein binding is decreased leading to higher levels of unbound or “free” drug available for pharmacological activity due to competitive binding of drugs to bilirubin, which is elevated in neonates verses albumin, the major plasma protein. The displacement of drugs from bilirubin can lead to CNS toxicity as the blood brain barrier is immaturely developed in neonates leading to significantly higher levels of drugs in the CNS.

**Metabolism**

Metabolism occurs primarily in the liver, but can also occur in the gastrointestinal tract, lung, kidney, and skin. Developmental changes in the drug metabolizing enzymes can lead to significant differences in the absorption and elimination (clearance) processes of the drugs (6,9). Metabolism of drugs which contributes to half of fatal adverse reactions in neonates and infants is significantly impaired in neonates since this pediatric sub-population has cytochrome P450 content 50 percent that of adult levels. But, between ages 2-4 years, P450 levels increase sharply as the liver weight increases significantly as compared to the total body weight. This leads to increased clearance or metabolism of drugs in infants and children than adults. Therefore, if higher doses of the same dosage form are given to infants and children, then the exposure to the excipients is pronounced in infants and children than in adults (10).

**Excretion**

Excretion of drugs show variability in the pediatric population with glomerular filtration rate (GFR) reaching 0.5 percent of adult levels in neonates. The GFR increases from 2-24 months of age with increased renal clearance of drugs. Hence, in infants and toddlers, increased clearance of drugs than in adults can lead to significantly lower plasma concentration of drugs available for therapeutic activity (6,11). Such variability in ADME properties between pediatric population and adults can have profound effects on the therapeutic endpoint of a drug. Since, not all excipients are pharmacologically ‘inert’, an excipient that may have been considered safe in adults may not be tolerated in pediatric population as seen with certain dyes such as tartrazine that has been casually linked to cause hyperactivity in children (12).

| Table 2. Classification of pediatric population based on age, average weight and ADME profile. |

**CHEMICAL REACTIVITIES AND TOXICOLOGICAL PROFILE OF EXCIPIENTS**

It is well known that certain classes of excipients produce incompatibilities with the API or interact with intracellular chemicals to produce adverse reactions. The interactions thus produced due to drug-excipient, excipient-excipient, or excipient-intracellular chemicals can be pronounced in pediatric population and in many cases interfere with normal growth and development processes (13). Though screening for drug-excipient or excipient-excipient interactions is a part of the preformulation process, the effect of such interactions has not been exhaustively evaluated in pediatric population.

Some of the common side effects resulting from excipients are highlighted in Table 3. Excipient incompatibilities can be a result of physical and chemical interactions. The focus of this manuscript is on chemical interactions that can impact pediatric growth and development process. Interactions between primary amines and carbohydrate-derived carbonyl group present in sugars such as dextrose, lactose leading to Maillard reaction (14), the formation of an imine and finally undergoing Amadori rearrangement is a classic example of such chemical incompatibilities due to excipients (Table 3).

Maillard reaction is known to occur in infants due to carbohydrate-derived carbonyl groups present in milk-based infant formulas and protein amino groups (15).
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These byproducts of Maillard reaction can function as electrophiles and cause adverse reactions in new-borns 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 (16, 17).

The use of buffering agents to stabilize pH sensitive drugs can be lead to incidents of gastro-oesophageal reflux (GOR) and gastro-oesophageal reflux disease (GORD) in neonates as gastric acid output of the stomach reaches maturity and approaches adult levels only by 3 months of age (18). Magnesium stearate is a commonly used lubricant in oral dosage forms.

There are numerous reports in the literature on the chemical incompatibilities of magnesium stearate with aspirin and drugs containing acetyl groups resulting in formation of salicylic acid, acetyl salicylic acid and salicylic acid.

A casual link between aspirin related drugs and Reye’s syndrome, which is characterized by hypoglycemia, hypoketonia, elevated ammonia, and organic aciduria in pediatric population, has long been established (19). Despite numerous reports of incompatibilities magnesium stearate continues to be a widely used lubricant in oral dosage forms. Alcoholic solvents such as sorbitol, propylene glycol, PEG and others are known to produce gastrointestinal disturbances in new-borns and infants above certain concentration threshold (20).

These alcohols are known to be absorbed from gastrointestinal tract and metabolized by the liver to pyruvic acid and lactic acid (20). Since new-borns and infants have immatured and developing epithelial barriers and drug metabolizing enzymes, the absorption of sorbitol, a polyol, is limited, but enhanced in the presence of glucose and fatty acids. The accumulation of sorbitol in the body of new-borns and infants has been implicated in diabetic-like symptoms in the body such as retinopathy. Since the amount of excipient in the formulation can play a critical role in bioavailability, efficacy and ultimately toxicity of the excipient and the API, the Allowable Daily Intake of the excipients in pediatric population along with the dose level that produces no observable adverse event (NOAEL), and adverse effects of the excipients have been referenced in Table 3.

RECOMMENDATIONS

No excipient is inert and above a certain concentration can produce adverse reactions in the pediatric population. Based on the FDA/CDER guidance document of 2005, pharmaceutical companies have taken into consideration the changing ADME profile of the pediatric age group to prepare suitable pediatric formulations that are both safe and efficacious.

Substitutions to the commonly used excipients for pediatric formulations can be made that include the reduction or elimination of preservatives such as thimerosal, benzyl alcohol, and propylene glycol from vaccines and formulations 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 percent), bronopol (2-bromo-2-nitropropane-1,3-diol), sodium azide, or 2-phenoxyethanol. In addition, use of single-dose vials is recommended in many instances to prevent the use of preservatives such as thimerosal or sulfites such as sodium metabisulfite.

Sorbitol, a commonly used sweetener in pediatric formulations, is another example of an excipient that causes gastrointestinal disorders such as abdominal pain, bloating, vomiting, and diarrhea when used in high concentrations (8, 12, 20). In young infants, sorbitol accumulation can also lead to diabetic complications such as retinopathy and cataracts. Therefore, amount of sorbitol is limited to 0.3 gm/kg in pediatric formulations (8, 12, 20). Aspartame is another artificial sweetener that has been replaced by stevia, date sugar, maple sugar, maple syrup molasses, and agave nectar in pediatric formulations.

Table 3. Allowable daily intake (adi) in children, no observable adverse event level (NOAEL), adverse effects of pharmaceutical excipients in the formulations.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>ADI Values</th>
<th>NOAEL</th>
<th>Adverse Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colorants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safranine O</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Intestinal absorption, long term effect not known, should not be used in children &lt; 2 yrs</td>
<td>20</td>
</tr>
<tr>
<td><strong>Solvents/ Co-Solvents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl Alcohol (BA)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Toxic syndrome observed in vaccines attributed to the practice of “flushing out” voluminous carriers with a solution containing BA.</td>
<td>9, 20</td>
</tr>
<tr>
<td>Ethyl Alcohol</td>
<td>Max 10% (12 yr)</td>
<td>Max 5% (5-12 yr)</td>
<td>Max 0.5% (6 mo)</td>
<td>Due to high blood brain barrier permeability, CNS effects and 0.1% limit</td>
</tr>
<tr>
<td>Peanut Oil</td>
<td>Not specified</td>
<td>Not specified</td>
<td>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 hrs compared with adults, 5 hrs</td>
<td>9, 20</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>35 mg/kg</td>
<td>Not specified</td>
<td>Use in infant formulas and topical preparations can lead to liver episodes of hyperammonemia</td>
<td>9, 20</td>
</tr>
<tr>
<td><strong>Sweeteners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartame</td>
<td>40 mg/day</td>
<td>Not specified</td>
<td>Causes of phenylketones, can cause phenylketonuria, hypoplasia in children but unknown</td>
<td>3, 20</td>
</tr>
<tr>
<td>Lactose</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Diarrhea, gas, loss of appetite or vomiting</td>
<td>15, 20</td>
</tr>
<tr>
<td>Saccharin</td>
<td>5 mg/day</td>
<td>Not specified</td>
<td>Hypersensitivity reactions (mainly dermatological) and potential risk to allergy to sulphites should avoid saccharin.</td>
<td>14, 20, 21</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>0.3 g/kg</td>
<td>Not specified</td>
<td>Maltose, gi distress</td>
<td>6, 12, 20</td>
</tr>
<tr>
<td>Sucrose</td>
<td>5 mg/kg/day</td>
<td>20 mg/kg/day</td>
<td>Not specified</td>
<td>6, 12, 20</td>
</tr>
<tr>
<td><strong>Surface Actives</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Polyoxyethylene 80</td>
<td>10 mg/kg/day</td>
<td>Not specified</td>
<td>Z-Fox syndrome (Homeobox gene, oral clefts, dysplasia, cataracts, hemivertebrae, anal atresia, hypoplastic and metacarpal anomalies in low birthweight infants)</td>
<td>14, 22</td>
</tr>
<tr>
<td>Polyoxyethylene</td>
<td>0.60 mg/kg</td>
<td>Not specified</td>
<td>Not specified</td>
<td>14, 22</td>
</tr>
<tr>
<td><strong>Preservatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoic acid</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Potassium benzoate</td>
<td>Up to 5 mg/kg</td>
<td>Not specified</td>
<td>Hepatotoxicity and contact urticaria</td>
<td>1, 20</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Up to 5 mg/kg</td>
<td>Not specified</td>
<td>Hepatotoxicity and contact urticaria</td>
<td>1, 20</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Sodium benzoate should be used cautiously and only where appropriate</td>
<td>1, 20</td>
</tr>
<tr>
<td>Thiosalicylate</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Sodium benzoate should be used cautiously and only where appropriate</td>
<td>1, 20</td>
</tr>
<tr>
<td><strong>Plasticisers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diethyl phthalate (DEP)</td>
<td>&lt;0.1 mg/kg</td>
<td>Not specified</td>
<td>Endocrine disruption, disrupt synthesis, sex, transport, binding, action or elimination of natural hormones in the body</td>
<td>23</td>
</tr>
<tr>
<td>Di-2-ethylhexyl phthalate (DEHP)</td>
<td>0.02 mg/kg</td>
<td>Not specified</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>
readily metabolized by lactase, leading to the buildup of lactic acid, hydrogen and carbon dioxide. Symptoms such as severe abdominal pain, flatulence, distention or bloating, and diarrhea, in addition to systemic symptoms such as muscle and joint pain and eczema can occur in infants and children [15, 20]. Sometimes children have very severe and prolonged reactions to lactose which can lead to further complications such as dehydration, bacterial proliferation, and metabolic acidosis. 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.

Phthalates play a critical role as a coating agent (plasticizer) in modified-release formulations, are used as containers for storing chemicals, and found in toys, have been implicated in developmental abnormalities in growing infants and children [23]. Exposure of phthalates to the fetus has been linked to developmental abnormalities such as cleft palate and skeletal malformations, and fetal death. Therefore, in March 2012, US FDA has released a draft guidance document for the pharmaceutical industry seeking to "Limit the use of certain phthalates as excipients including DBP and DEHP in CDER-regulated products" [24].

Due to the health risks of certain phthalates, the guidance document recommends avoiding DBP and DEHP as excipients in nonprescription and prescription medications. Most regulatory agencies around the world restrict the use of coloring agents such as tartrazine, since the azo dyes have been linked to hypersensitivity reactions and ADHD in children. Such dyes can be substituted with vegetable dyes such as annatto, malt beta-carotene and turmeric or not used at all in pediatric formulations. In conclusion, excipients for pediatric formulations should be carefully selected with reference to the age of the pediatric population, ADME developmental changes, and duration of treatment to ensure safety and efficacy of such formulations in pediatric population.

REFERENCES AND NOTES

23. FDA Food Additives permitted for direct addition to food for human consumption 21 CFR part 172.