Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review

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Abstract

Objectives This review focuses on the recommended strategies for the oral administration of paediatric medicines with food in the context of their biopharmaceutical properties.

Key findings Acceptability of oral medicines in young patients is more challenging than in adult patients. Mixing oral dosage forms with foods and drinks is sometimes suggested to administer a specific dose and enhance compliance in the paediatric population. In this review, the strategies for the co-administration of paediatric medicines with food and drinks are discussed. Current administration practices as reported by healthcare professionals and parents/carers are compared with the relevant guidelines. Differences in the type of vehicles recommended to be used and actually used in current practice were identified. Correlations of the type of food recommended, the type of formulation and the drug’s biopharmaceutical classification system (BCS) class were performed and revealed that recommendations should be made on a case-by-case basis.

Summary The propensity for physiochemical or bioavailability changes that may occur from the co-administration of medicines with food and drinks in the paediatric population should be considered, and harmonisation of the recommended administration strategies is needed.

Introduction

Historically, medicines for children have not been designed and tested for each target subpopulation. Medicines developed for adults are commonly administered to the paediatric population, usually informally adapted and in the absence of relevant evidence.\(^{[1]}\) It is widely recognised though that ‘children are not just small adults’\(^{[2]}\); constant developmental changes, in terms of anatomical and physiological aspects until adulthood, need to be considered for an efficient treatment and the development of appropriate formulations.

The use of unlicensed and off-label medicines for children is widespread, with healthcare professionals, parents or carers facing the need to manipulate medicines designed for adults.\(^{[3]}\) This manipulation that can range from simple (e.g. tablet splitting) to complex methods (e.g. tablet crushing for suspension preparation) results in the availability of formulations ready to be administered and appropriate for the condition and patient intended. Appropriate oral formulations for young patients need to overcome swallowing difficulties or undesirable palatability, which could affect adherence in these patients.\(^{[3–6]}\)

Acceptability, defined as the overall acceptance of the dosage form regardless of the mode of its administration,\(^{[7]}\) has been identified as an integral part of the paediatric formulation development. It depends on several factors, such as suitability of the dosage form and palatability of the oral medicine. Palatability, described as the overall acceptance of the taste, flavour, smell, dose, volume or size and texture of a medicine to be administered by mouth or to be swallowed, is essential for adherence in this population and influences the choice of dosage form and its design.\(^{[7]}\) Carers usually attempt to facilitate administration and improve the acceptance of the patient by mixing the dose with food or drinks.\(^{[8,9]}\) If this situation is intended/predicted,
appropriate compatibility studies should be conducted to evaluate possible changes in bioavailability and information should be provided in the patient information leaflet, by the manufacturer.\textsuperscript{[3]} Recent studies have shown that sometimes this type of co-administration is performed without following the appropriate procedures, for example by letting the child or carer choose the food or drink used for administration without proof of safety and efficacy.\textsuperscript{[8,9]}

This review describes the current strategies employed to overcome administration of a specific dose, acceptability and adherence issues of medicines in the paediatric population, focusing on the co-administration of medicines with food and drinks. Current administration practices as reported by healthcare professionals and parents/carers are compared with the relevant guidelines to assess the possible clinical consequences of these practices, in particular changes in the bioavailability of the drug. The type of food and drinks co-administered with paediatrics medicines was correlated for the first time with the type of formulation and the drug’s biopharmaceutical classification system (BCS) class to reveal the biopharmaceutical aspects of the recommended administration strategies.

### Age classification of paediatric patients

Children differ from adults in a biological and pharmacological development perspective, and these differences should be reflected in the development and use of medicines for the paediatric population. Moreover, and although often overlooked, due to continuous physiological growth and maturation, the paediatric population is not a homogeneous group and can be subdivided accordingly to specific age groups. The division of this population in specific age groups is not harmonised between all the regulatory authorities, and some differences are observed in the upper age limit and in the distinction between young children and older children and premature and term newborns.\textsuperscript{[10–13]} In this review, the classification identified by the International Conference on Harmonization of Technical Requirements for registration of Pharmaceuticals for Human Use\textsuperscript{[12]} is followed (Table 1).

<table>
<thead>
<tr>
<th>Paediatric subgroup</th>
<th>Name used</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm newborn infants</td>
<td>&lt;37 weeks gestation</td>
<td></td>
</tr>
<tr>
<td>(‘Prematures’)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term newborn infants</td>
<td>Neonates</td>
<td>0–27 days</td>
</tr>
<tr>
<td>(‘Neonates’)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants and toddlers</td>
<td>Infants</td>
<td>28 days–24 months</td>
</tr>
<tr>
<td>Children</td>
<td>Children</td>
<td>2–11 years</td>
</tr>
<tr>
<td>Adolescents</td>
<td>Adolescents</td>
<td>12–16 or 18 years (depending on region)</td>
</tr>
</tbody>
</table>

### Paediatric formulations: from regulatory guidance to reality

#### Regulatory status

Developing paediatric formulations as acceptable dosage forms, with a predictable and safe drug release in the patient and ensuring compliance, is scientifically challenging due to unique requirements and limitations.\textsuperscript{[1,14]} The paediatric population represents a small target group with many short term illnesses, and the development of acceptable formulations can differ significantly from the adult formulations in terms of the excipients that can be used and the selected route of administration.\textsuperscript{[4,14]}

New regulations, additional funding opportunities and innovative collaborative research initiatives both in the USA (Best Pharmaceuticals for Children Act – BPCA, and the Pediatric Research Equity Act – PREA\textsuperscript{[15,16]}), and the European Union (‘Better medicines for children’ concept paper and the Paediatric Regulation (EC) No. 1901/2006, which introduced Paediatric Use Marketing Authorization – PUMA – and Paediatric Investigation Plan – PIP\textsuperscript{[11,17]}), have affected the paediatric formulation development. Novel formulations, such as flexible, dispersible and multiparticulate oral solid dosage forms, have started to appear. The paradigm shift towards oral solid formulations of appropriate size and properties (i.e. sprinkles, multiparticulates) has enabled greater dose flexibility, easier administration and better acceptability of drug formulations, while efficacy and safety are maintained. Overcoming swallowability, and taste and texture issues of the drug formulation is a current challenge to achieve paediatric compliance.\textsuperscript{[4]} Co-administration with food and drinks is often recommended to facilitate ingestion, but it may have an impact on the solubility and oral bioavailability of the drug, and the risk of medication errors is increased.\textsuperscript{[9,18,19]}

The European Medicines Agency highlights the need for appropriate testing to support formulation changes during paediatric formulation development, the importance of changes in bioavailability when extemporaneously manipulating a solid dosage form by mixing with food and drinks and the impact of physiology on the absorption potential from modified release formulations.\textsuperscript{[2]} Furthermore, any formulation changes undertaken for the development of an acceptable and safer or more effective formulation for different paediatric age groups should be included in the paediatric investigation plan.\textsuperscript{[20]}

Legislative and regulatory frameworks, which underpin the expectation that children will be given the medicines they deserve, have been established in two major
Use of off-label and unlicensed medicines in the paediatric population

The frequency of use of off-label and unlicensed medicines in children in the United Kingdom (UK) is ~11% in general practice,[21] 25% in hospital general wards,[22] 40% in paediatric intensive care units,[23] and 80% in neonatal intensive care units.[24] This trend is similar in other European jurisdictions (EU and USA). However, scientific evidence to guide paediatric formulation development is still lacking, with data and experience acquired by individual pharmaceutical companies during product development not always available in the public domain.

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Adherence to prescribed medication varies between 11% and 93% among the paediatric population (median value of 58%) and is lower than the one reported in adults (30–70%).[29–31] Formulation acceptability facilitates adherence to medication in children and the achievement of intended treatment outcomes.[6] Variability of acceptability of dosage form(s) in young patients relates to individual characteristics (age and individual health status, behaviour, disabilities and background), difficulties in medicines' administration (manipulation of medicines and taste), medication-taking behaviour (influence of family, school and life situation/context) and culture.[3,4,7]

Individual characteristics

A paediatric patient cannot be standardised. According to physical development and psychological understanding, the ability to use different dosage forms can vary greatly. The age at which children can safely swallow solid oral dosage forms depends on health status and interpatient differences.[4]

Disease status

The type of disease, acute or chronic, as well as the duration of treatment and the required number of medicines, affects acceptability of medicines. Paediatric patients who are acutely unwell may be frightened and less cooperative than usual, especially if in pain or with fever. Sometimes medications have to be administered during school hours and training of the carer is required. Paediatric patients with long-term illness requiring continuing medication can be trained to take solid dosage forms from a relatively early age of 3–5 years, whereas for younger children, training is given to carers.[7,9]

Carers

Dependence on a carer is common for the majority of the paediatric age groups with the exception of adolescents. The willingness and ability of the carer influence the acceptability of the medicine and treatment outcome.[6] Attention
should be given to the ease of administration by the carer as it impacts on dosage form choice and adherence.\(^3\)\(^,\)\(^9\) Moreover, carers may follow different administration techniques in the domiciliary/pragmatic environment than the ones recommended to them by healthcare professionals.\(^3\)\(^2\)

**Adolescence and peer pressure**

Information on handling medicinal products during puberty is scarce.\(^7\) Adolescents are usually responsible for their own medicine administration and capable of taking medication without mixing it with food or drinks. They may be rebellious though and reject medicinal products they have previously taken or be affected by peer pressure or recalcitrance. Life style changes also may impose the need for discrete and portable dosage forms.

**Cultural and geographical differences**

The acceptability of medicines can be influenced by the location or setting in which the administration takes place. Interpretation of colour, form and taste of the medicine linked to strength and effect presents sociocultural variability. For example, a large pill can be interpreted as stronger than a small one or a bitter tasting medicine as more powerful than a sweet one. Traditional homeopathic or herbal medicines are preferred in some societies instead of western medicines that are viewed as ‘too strong’ or with ‘too many’ side effects.\(^3\)\(^3\) Traditional beliefs, misconceptions and irrational use of medicines, may be more pronounced in resource-poor settings (education) and where other services are limited (i.e. access to clean water). The preferred method for dispensing extemporaneous preparations relates to the country; for example, in the UK, Ireland and Norway, oral liquids tend to be prepared, whereas in France and Spain capsules are usually chosen, and in Italy, powders are preferred.\(^2\)\(^6\) Differences in the palatability and acceptability of different routes of administration in different countries and different religions are well recognised, even though data for evaluation of the effect of global sociocultural differences on adherence to paediatric medicines are limited.\(^3\)\(^3\)

**Palatability**

Children have a low tolerance for disagreeable taste, smell and texture which affects their adherence to oral formulations. Size, taste and texture have been found to be the most significant factors controlling the drug administration to children.\(^8\)\(^,\)\(^9\) To overcome poor taste, and to improve acceptability to paediatric patients, a wide range of drugs are mixed with food before administration.\(^9\)

**Improving palatability and acceptability: mixing medication with food or drinks**

**Current practice and legislation**

Mixing medication with food or drinks intends to mask the unsatisfactory palatability of a formulation, in cases that it cannot be further improved through dosage form design, and to enhance acceptability through swallowing facilitation or texture improvement. Children often struggle with dysphagia either because the tablet or capsule is ‘too large’ to swallow or the liquid is ‘too bitter’ or ‘unpleasant’. Therefore, carers mix the medication (usually after manipulation of the initial dosage form) with a drink (e.g. fruit juice) or with food (e.g. yoghurt or applesauce).\(^7\)\(^,\)\(^9\)\(^,\)\(^3\)\(^4\) This is particularly prevalent in children with neurological impairments and mental health difficulties, as the majority of psychoactive medicines are unlicensed in children and have a bitter taste.\(^8\) In a recent study conducted in a large paediatric population suffering from different chronic conditions manipulation of the formulations in the domiciliary environment reported by almost one-third (74/252) of respondents was mainly associated with the age of child, socio-economic status, taste, texture, and volume/or quantity of dosage form. 19% (94/499) of formulations were manipulated with the majority of these (93%, 87/94) to be manipulated ‘always’ (i.e. before every dose administration).\(^3\)\(^2\)

Current legislation highlights that whatever the reason for mixing medicines with food or drinks is, the rationale should be discussed and justified, and relevant information should be included in the summary of product characteristics (SmPC) and patient information leaflet (PIL).\(^7\) Clear instructions on the type of food and drinks appropriate for mixing with the paediatric medicine should be given. Appropriate warnings in cases when such practice is unsuitable or has not been studied must be provided. Any mixing outside the recommendations is responsibility of the healthcare professional or the user.\(^3\)\(^,\)\(^7\) Instructions on the quantity of the food or drinks to be used and the acceptable time period after mixing based on the chemical stability of the drug should be noted. If chewing of the product is expected to alter product performance or influence acceptability, it must be clearly stated.

Different food or drinks can have different effects on the paediatric medicine due to their properties, such as pH, osmolality and viscosity. For example, pudding and applesauce are both considered as a ‘soft food’, but they had a different effect on drug’s absorption when mixed with the same drug.\(^3\)\(^5\) The possible effect of food or drinks on the biopharmaceutical characteristics of the medicinal product
and on its acceptability, compatibility and stability should be studied. Assessment of the impact of food and drinks on drug’s bioavailability may be extrapolated from studies in adults, if relevant to the paediatric medicine, for example adult food effect studies and achlorhydria studies.

Current platforms

National or regional formularies (quite often hospital formularies) are used for paediatric medicines, especially in cases where effective adult doses of newly approved medicines cannot be down-scaled based on a simplistic body weight extrapolation. In the UK, the British National Formulary for Children (BNF-C) was established in 2006 to compile available information and harmonise practice. The BNF-C lists the correct mode of administration of paediatric medicines, with recommendations for mixing the drugs with food or drinks, when applicable. In practice, several hospital formularies are used with recommendations for mixing paediatric medicines with food or drinks, some of which are not recorded in the BNF-C.

For the purpose of this review, both the BNF-C and the Guy’s and St. Thomas, King’s College and University Lewisham Hospitals’ Paediatric Formulary were consulted, to access the drugs recommended to be mixed with food or drinks before oral administration, and compare differences between these formularies (Table 2). 61 drugs are recommended to be mixed with food or drinks before administration. Differences in the instructions between the two sources are observed and only 30 drugs are included in both formularies although sometimes with different recommendations; for example, sodium phenylbutyrate is recommended to be mixed with meals or milk in the hospital formulary but not in the BNF-C. A more concerning issue arises in the case of tenofovir disoproxil, as the BNF-C warns against mixing with liquids whereas in the hospital formulary mixing of the granules with orange juice or water is advised. The BCS class of the drug was added (information not included in the formularies). The paediatric age subgroups were classified as Neonates, Infants, Children and Adolescents (Table 1). Seven formulation types were identified: tablets crushed before mixing, opened capsules whose contents are sprinkled on or mixed with the food or drink, ampoules for IV administration which are recommended to be diluted and administered orally, granules, powder, solutions and suspensions. The type of food or drinks recommended was categorised in ‘soft foods’, ‘meals’, ‘juice’, ‘milk’, ‘water’ and ‘others’. ‘soft foods’ include yoghurt, applesauce, jam, honey or ice cream; ‘milk’ refers to particular types as breast or skimmed milk; ‘juices’ are fruit, apple, orange, blackcurrant or squashes and ‘others’ refer to cola or tea. Specific vehicles recommended are included in the ‘notes’ column. Recommended administration in water was noted in the cases where water was an alternative vehicle to other drinks. Drugs for which it was noted that tablets ‘may be crushed or dissolved’ without specific suggestion for the vehicles are not included.

Biopharmaceutical properties of drugs and mixing with food and drinks

The biopharmaceutical characteristics of the medicinal product will be affected by its mixing with food or drinks. An analysis was performed to reveal potential correlation of the biopharmaceutical properties of the drugs with the age group, the type of formulation administered and the type of food and drinks used for the mixing with the drug.

The BCS established by Amidon et al., categorising drugs based on their solubility and permeability, is a regulatory framework for oral drug products for adults. Of the 61 drugs listed (Table 2), 44% could not be assigned to a BCS class based on the published information regarding their solubility and permeability, of the remainder 25% belong to BCS class 1, 20% to BCS class 2, 8% to BCS class 3 and 3% to BCS class 4 (Figure 1). It is worth noting that the majority of drugs suggested to be co-administered with food and drinks are drugs with high permeability.

Biopharmaceutical classification system class of the drug vs age group

The relationship between the paediatric age group and the BCS class of the drug is presented in Figure 2. The majority of drugs recommended to be given with food or drinks to neonates are BCS class 1 drugs. From the drugs identified from the two formularies studied, there are no drugs belonging to BCS class 3 or 4 suggested to be mixed with foods or drinks to neonates. For infants, drugs recommended to be mixed with food or drinks are drugs belonging to all BCS classes with the exception of BCS class 4 drugs. Regarding the other two subpopulations (children and adolescents), from the analysis performed, it can be observed that drugs from all four BCS classes are indicated to be mixed with foods or drinks (Figure 2).

Biopharmaceutical classification system class of the drug vs type of formulation

In Figure 3, the relationship between the drug’s BCS class and the type of formulation administered and mixed with food or drinks is shown. Capsules and tablets are the most common formulations used in this practice for BCS class 1 and BCS class 3 drugs and solutions, capsules and tablets for BCS class 2 drugs. BCS class 4 compounds formulated as granules and solutions are the prevalent dosage forms mixed with foods or drinks.
<table>
<thead>
<tr>
<th>Drug</th>
<th>BCS classification</th>
<th>Age</th>
<th>Formulation type</th>
<th>Soft food</th>
<th>Meals</th>
<th>Juice</th>
<th>Milk</th>
<th>Water</th>
<th>Others</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcysteine (A) (B)</td>
<td>I (57)</td>
<td>N I C A</td>
<td>Granules; ampoule*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: blackcurrant, orange Others: cola, orange or blackcurrant syrup</td>
</tr>
<tr>
<td>Betaine (A) (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Powder</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Meals: formula, (+)</td>
</tr>
<tr>
<td>Budesonide (A)</td>
<td>II (58)</td>
<td>A</td>
<td>Capsule</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>Juices: apple, orange Others: (should be mixed thoroughly to avoid precipitation)</td>
</tr>
<tr>
<td>Calcium carbonate (A/B)</td>
<td>–</td>
<td>N</td>
<td>Tablet; solution</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Calcium Polystyrene Sulfonate (A) (B)</td>
<td>–</td>
<td>I C A</td>
<td>Powder</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>Others: soft drinks (should not be given with squash or fruit juice)</td>
</tr>
<tr>
<td>Carnitine (l-carnitine) (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Solution</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: fruit Others: soft drinks (e.g. caffeine-free diet cola)</td>
</tr>
<tr>
<td>Charcoal, activated (A)</td>
<td>–</td>
<td>N I C A</td>
<td>Suspension; capsule; tablet</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Chloral hydrate (A)</td>
<td>–</td>
<td>N I C A</td>
<td>Solution; tablet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Cholestyramine (A) (B)</td>
<td>–</td>
<td>I C A</td>
<td>Powder</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Soft foods: pulpy fruits, thin soups Others: liquids</td>
</tr>
<tr>
<td>Cyclosporin (A) (B)</td>
<td>II (59)</td>
<td>I C A</td>
<td>Solution</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: orange, apple, squash (should not be mixed with blackcurrant juice)</td>
</tr>
<tr>
<td>Clindamycin (B)</td>
<td>II (60)</td>
<td>N I C A</td>
<td>Capsule</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Cholecalciferol (A)</td>
<td>–</td>
<td>I C A</td>
<td>Solution</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Soft foods, meals: cold or lukewarm</td>
</tr>
<tr>
<td>Colestipol hydrochloride (A)(B)</td>
<td>–</td>
<td>A</td>
<td>Granules</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Soft foods: thin soups, pulpy fruits, yoghurt Others: liquids</td>
</tr>
<tr>
<td>Cyclophosphamide (B)</td>
<td>II (58)</td>
<td>b</td>
<td>Ampoule*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: fruit Others: skimmed Others: cereals</td>
</tr>
<tr>
<td>Deferasirox (A) (B)</td>
<td>II (61)</td>
<td>I C A</td>
<td>Dispersible tablet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: apple, orange Others: breastmilk, (+)</td>
</tr>
<tr>
<td>Didanosine (A)</td>
<td>II (58)</td>
<td>I C A</td>
<td>Chewable tablet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: apple Others: (should not be mixed with feed thickeners)</td>
</tr>
<tr>
<td>Docusate sodium (A) (B)</td>
<td>–</td>
<td>I C A</td>
<td>Solution</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: squash Others: (should be mixed with feed thickeners)</td>
</tr>
<tr>
<td>Efavirenz (B)</td>
<td>II (62)</td>
<td>C A</td>
<td>Capsule</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Enoximone (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Ampoule*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meals: formula Others: strong tasting liquid</td>
</tr>
<tr>
<td>Fosamprenavir (B)</td>
<td>II (63)</td>
<td>C A</td>
<td>Suspension</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Gabapentin (B)</td>
<td>II (64)</td>
<td>C A</td>
<td>Capsule</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: blackcurrant Others: strong tasting liquid</td>
</tr>
<tr>
<td>Gaviscon (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Powder</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(should not be mixed with feed thickeners)</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride (A)</td>
<td>–</td>
<td>A</td>
<td>Capsule (IR or MR)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Imatinib (A)</td>
<td>II (65)</td>
<td>I C A</td>
<td>Tablet</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Juices: apple Others: (should not be mixed with feed thickeners)</td>
</tr>
</tbody>
</table>

Table 2 Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>BCS classification</th>
<th>Age</th>
<th>Formulation type</th>
<th>Mixed with</th>
<th>Soft food</th>
<th>Meals</th>
<th>Juice</th>
<th>Milk</th>
<th>Water</th>
<th>Others</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine (A) (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Solution</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Labetalol hydrochloride (A)(B)</td>
<td>–</td>
<td>N I C A</td>
<td>Ampoule&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: squash</td>
</tr>
<tr>
<td>Lactulose (A)(B)</td>
<td>I C A</td>
<td></td>
<td>Solution; powder</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Mix with food/drinks to reduce nausea</td>
</tr>
<tr>
<td>Lisdexamfetamine mesilate (A)</td>
<td>–</td>
<td>C A</td>
<td>Capsule</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Soft foods: yoghurt, juices: orange</td>
</tr>
<tr>
<td>Magnesium aspartate (A)</td>
<td>–</td>
<td>I C A</td>
<td>Powder; granules</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: orange, Others: tea</td>
</tr>
<tr>
<td>Mefloquine (A)</td>
<td>I [67]</td>
<td>I C A</td>
<td>Tablet</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Megalumine amidotrizoate with sodium amidotrizoate (A)</td>
<td>–</td>
<td>I C A</td>
<td>Solution</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: fruit</td>
</tr>
<tr>
<td>Mercaptopine (A) (B)</td>
<td>–</td>
<td>N I C A</td>
<td>Capsule</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Strongly flavoured drinks or food at a temperature suitable for eating (should avoid acidic drinks)</td>
</tr>
<tr>
<td>Mesalazine (A) (B)</td>
<td>N[66]</td>
<td>C A</td>
<td>Granules</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: orange</td>
</tr>
<tr>
<td>Mesna (A)(B)</td>
<td>–</td>
<td>C</td>
<td>Ampoule&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: orange, (+) Others: cola, (+)</td>
</tr>
<tr>
<td>Metformin (B)</td>
<td>I [64]</td>
<td>C A</td>
<td>Powder</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: orange, Water: sparkling, Others: cola</td>
</tr>
<tr>
<td>Methylphenidate hydrochloride (A)(B)</td>
<td>I[58]</td>
<td>C A</td>
<td>Capsule (MR)</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Soft foods: applesauce</td>
</tr>
<tr>
<td>Midazolam (A)(B)</td>
<td>I[65]</td>
<td>I C A</td>
<td>Ampoule&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: apple, blackcurrant, Others: cola, chocolate sauce</td>
</tr>
<tr>
<td>Montelukast (A)(B)</td>
<td>I[70]</td>
<td>C A</td>
<td>Granules</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Soft foods: cold or at room temperature (not liquid)</td>
</tr>
<tr>
<td>Morphine (A)</td>
<td>I[56]</td>
<td>N I C A</td>
<td>Capsule (MR)</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Olanzapine (A)</td>
<td>I[55]</td>
<td>A</td>
<td>(Oro)dispersible tablet</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Juices: apple, orange, Others: coffee</td>
</tr>
<tr>
<td>Omeprazole (A)</td>
<td>I[66]</td>
<td>N I C A</td>
<td>Tablet (GR); Capsule</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Soft foods: yoghurt, Juices: fruit</td>
</tr>
<tr>
<td>Pancreatin (A)(B)</td>
<td>–</td>
<td>N I C A</td>
<td>Granules (GR); Capsule</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>Soft foods: acidic, jam, (+) Meals: formula Juices: apple, Others: acidic soft drinks</td>
</tr>
<tr>
<td>Potassium iodide (B)</td>
<td>I[61]</td>
<td>N I</td>
<td>Capsule</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Progesterone hydrochloride (A)(B)</td>
<td>I[61]</td>
<td>N I C A</td>
<td>Tablet</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Soft foods: jam, Others: honey, (+)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Juices: fruit
<sup>b</sup> Strongly flavoured drinks or food at a temperature suitable for eating (should avoid acidic drinks)
<sup>c</sup> Juices: apple, blackcurrant, Others: cola, chocolate sauce
<sup>d</sup> Soft foods: cold or at room temperature (not liquid)
<sup>e</sup> Juices: apple, orange, Others: coffee
<sup>f</sup> Soft foods: acidic, jam, (+) Meals: formula Juices: apple, Others: acidic soft drinks
<sup>g</sup> Soft foods: jam, yoghurt, honey, (+)
As illustrated in Figure 4, juice is the most prevalent type of vehicle used for drugs belonging to all the BCS classes. Soft foods are commonly recommended for mixing with BCS class 1 and 2 drugs, milk with BCS class 4 drugs, whereas meals are the less commonly suggested vehicles to be mixed with paediatric medicines. The characteristics of the vehicles may have an impact on drug's stability and solubility compromising its bioavailability and therapeutic outcomes. For example, most fruit juices and cola due to their low acidic pH can affect the stability of certain API's. Mixing soft foods such as ice cream, with BCS class 2 drugs (lipophilic drugs), could have an effect on drug's solubility due to partitioning into the lipophilic phase. Variability on the outcome would be expected when drugs are mixed with different food or drinks belonging in the same food or drink 'type' due to the intravariability of the characteristics of vehicles of the same food or drink 'type'.

**Type of food vs type of formulation**

The relationship between the type of vehicle and the type of formulation is presented in Figure 5. Ampoules are recommended to be mixed either with juice or other types of drinks (tea or cola). When this practice is followed, the risk of precipitation due to dilution or pH of the liquid vehicle should be considered. Even though paediatric patients do not typically drink hot liquids, the effect of temperature when preparing a formula or tea on the stability of the drug should...
be studied. Soft foods or meals are suggested for the mixing with suspensions, and soft foods and juice for capsules and granules. All vehicles with the exception of soft foods are reported for the mixing with solutions, whereas tablets and dispersible tablets are recommended to be mixed with all the vehicles, without preference. Based on the drug’s and vehicle’s characteristics, the potential impact of the mixing practise on drug’s solubility and dissolution and subsequently on drug’s absorption should be explored. Viscosity, fat and dairy-protein content are other characteristics which apart from their effect on gastric emptying rate may also interfere with the drug’s behaviour and alter its bioavailability.

**Type of formulation vs age group**

The relationship between the formulation type and the age group is shown in Figure 6. For neonates, from the seven types of formulations identified in this study, only ampoules, capsule contents and suspensions are recommended to be mixed with food and drinks. For all the other groups, all the formulation types are accepted.

**Administration techniques reported by healthcare professionals and parents/carers**

Mixing medication with food or drinks is a common practise on paediatric wards with nurses being usually responsible for administering medication. In a recent study, it was found that the majority of paediatric nurses modify oral dosage forms or mix medication with food or drinks before administration. The most common food/drinks reported to be used were fruit yoghurts, crushed bananas and diluted and concentrated fruit juices. Co-mixing was
perceived as a time-consuming process, and preference was expressed for mixing the powdered dosage form(s) into juice or a liquid rather than into solid foods. The actual method used to mix the medication with the food/drinks was not consistent, with some interviewees reporting that they ‘poured the contents of the capsule/crushed tablet onto a spoon and added the food item to it’, while others reported that they ‘dispersed the powdered medicine directly into the food’.\[8\] In a survey performed in a hospital in Cape Town (South Africa) to investigate carers’ practices and perceptions regarding tuberculosis (TB) treatment of children, about two-thirds of the interviewees reported that TB medication was given after meals.\[34\] The medication was crushed, dissolved or mixed with food or drinks in over half of the cases, while 30% reported that medication was swallowed or chewed. It should be noted though that among the drug formulations commonly used for TB, only one brand of tablets can be chewed or dispersed in 5 ml of water. All other tablets are not dispersible, and for one of the tablet formulations, crushing has been associated with treatment failure due to reduced bioavailability of the drug.\[34,38\] Moreover, parts of crushed or dissolved tablets or contents of capsules may not be swallowed, resulting in administration of a lower dose than the intended one.

In another study, the ad hoc techniques that parents and carers had reported to healthcare professional groups, as well as the techniques that the healthcare professionals recommended to them for the paediatric medicines administration, were reviewed.\[9\] Nurses gave examples of what is actually done in the wards with yoghurt being the vehicle of preference, whereas medical practitioners described in detail the practice that the parents follow which does not always correspond to the practice on the wards. The majority of nurses were unaware of the potential drug stability and degradation issues when performing ad hoc administration techniques. Some of them were not conscious of the possible impact upon clinical outcome, with one nurse even saying ‘just try whatever the child likes’. Pharmacists expressed their concern regarding the impact of these techniques on drug’s pharmacokinetics, for example the effect
of acidic juice on drug’s solubility and absorption. The participating healthcare professionals were unaware of the level of evidence supporting the various drug/formulation manipulation techniques. The need for more information about drug-food compatibilities was revealed and training issues were identified as few nurses were aware of the pharmaceutical implications of this practice.

Parents/carers may not always follow the administration techniques recommended to them by healthcare professionals in the domiciliary environment, and it is not clear whether healthcare professionals are always aware of these practices.\cite{32}

**Effect of mixing medicines with food and drinks on drug’s bioavailability**

Combination of medication with food or drinks to mask the taste of the drug can have an effect on drug’s safety and efficacy. Even though potential treatment issues related to the crushing of modified release tablets or capsules are well recognised and understood, this does not seem to apply for issues associated with the crushing of other formulation types (e.g. immediate release formulations).\cite{39,40} Increased bioavailability or subtherapeutic drug levels due to loss of the dose during crushing and transfer of immediate release tablets have been observed.\cite{38,41–43} Crushing of tablets or opening of capsules with enteric coating could result in decreased drug absorption and efficacy or in irritation on gastrointestinal mucosa depending on the drug formulated.\cite{18} Drug loss through the crushing process is also a concern as children may receive reduced and variable dosing. Contamination issues may occur if a previously uncleaned vessel is used for the paediatric medicine administration. Assessment of drug pharmacokinetics in children with crushed tablets is performed under a ‘standardised’ method, that is using water for dissolving the drug and may not represent accurate, realistic daily preparation practices. Delivering medications with fruit juices such as grapefruit, orange or apple juice affects absorption of several drugs possibly due to their acidic pH and increased potential for drug precipitation or degradation.\cite{44,45} Alterations of physiological conditions such as gastric emptying, and of gastrointestinal contents’ properties such as viscosity, osmolality and calorific content after food administration, can affect drug’s pharmacokinetics.\cite{46,47} In some cases, crushing tablets or opening capsules and mixing with a small volume of soft foods did not alter bioavailability significantly.\cite{19,48} In other cases though, absorption was impaired when crushed tablets were mixed with pudding compared to the use of applesauce\cite{55} and absorption was delayed after mixing enteric-coated beads with yoghurt or applesauce.\cite{49} Comparative release and dissolution studies of four drugs from crushed and whole tablets in six different foods and drinks frequently used in the clinical setting revealed that the impact on drug’s dissolution depends on the drug properties and the vehicle properties.\cite{18} Furthermore, stability issues can arise when/whether there is a delay between preparation and administration.

Food–drug interaction studies are widely reported in adult populations, with dedicated regulatory guidance on the conduct of food effect clinical studies.\cite{10,50} For paediatric populations, the guidance surrounding food effect is limited.\cite{19} In USA, the ‘Pediatric Study Decision Tree’\cite{50} allows extrapolation from adult data sets if there is sufficient similarity of both the disease progression and the response to intervention between source and target population. If the exposure–response relationship of the medicinal product is similar, the only PK studies required in paediatric populations are those for dose determination and safety evaluation. Similarly in EU, EMA guidance states that relative bioavailability comparisons of paediatric formulations with the adult oral formulations should typically be conducted in adults with only dose selection pharmacokinetic studies required in paediatric populations.\cite{17,51} Therefore, the majority of paediatric pharmacokinetic studies are conducted in the fasted state with very limited pharmacokinetic studies in the fed state in which milk or standardised breakfasts are mainly used.\cite{19}

The extrapolation of food effects observed in adults into paediatric populations is an unexplored and complex area as there are key differences between both populations, namely:

- Biological and anatomical differences in the gastrointestinal tract;
- Different feeding patterns, both in terms of food composition and feeding frequency;
- Reduced volume ingested by younger patients that affects the gastric emptying rate and differences to the emptying rate observed in adult studies are expected.

The nature of the food utilised in common practice by carers in paediatric patients adds complexity to the extrapolation of the food effect from adults studies.\cite{34} Food effect can be different between paediatric and adult studies; for example, food effect was more marked in children compared to adults for sustained-release theophylline formulations with bioavailability in the fed state being lower in children than in adults.\cite{35}

**Conclusions**

A global effort to improve paediatric accessibility to medicines is observed, which in turn has increased the number of drugs tested in and labelled for use in children.\cite{1} Healthcare professionals, parents or carers face the
Biopharmaceutics of paediatric drugs with food

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need to manipulate an adult medicine and mix it with food or drinks before administration to improve palatability. Although there is some information available regarding drug manipulation and the subsequent effect on drug stability/degradation, until recently this information had limited relevance as it mainly considered administration via PEG (percutaneous endoscopic gastrostomy) tubes and not mixing with food. Points to consider would relate to the type of food used in the study in terms of acceptance from the paediatric population and its uniform composition in different countries. For example, studies have been performed with applesauce which is not very well accepted among the paediatric population and may differ in sugar content in different countries. Furthermore, viscosity of the vehicle affects dissolution and release aspects from crushed tablets. The pH of the vehicle affects drug’s stability. For example, the pH of fruit yoghurts that are commonly used vehicles could compromise the chemical stability of drugs that are acid sensitive, particularly in the case of manipulation of enteric-coated dosage forms.

The European Committee on Pharmaceutica1s and Pharmaceutical Care (CD-P-PH) and the European Directorate for the Quality of Medicines & HealthCare (EDQM) have recently launched an initiative to make a European Paediatric Formulary. This formulary will give easy access to hospital and retail pharmacies across Europe to monographs for the preparation of extemporaneous formulations for paediatric medicines, and the practice among all countries and regions can be harmonised. The inevitable use of deduction as a means to obtain what is ‘probably’ the best therapy for a child will gradually disappear, and the continuous production and availability of evidence-based information for health professionals and carers will lead to better therapeutic approaches.

References


36. Guy’s, St Thomas’s and Lewisham Hospitals. Guy’s, St Thomas’s and Lewisham Hospitals Paediatric Formulary, 9th edn. London: Guy’s & St Thomas’ NHS Foundation Trust, 2012.


