Pediatric Formulations: Child-Friendly Oral Dosage Forms

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• Children require different oral dosage forms from adults due to differences in swallowing abilities, taste preferences, and dosage requirements.

• The pediatric formulations available are generally liquids or powders for reconstitution.

• Extemporaneous formulations are a common workaround for the lack of commercially available preparations, but concerns regarding lack of dose accuracy, stability, and consistency in preparation present some difficulties for caregivers.
From the pediatricians' perspective, the availability of easy to swallow and palatable formulations can mean the difference between treatment success and failure.

The age at which children are able to swallow tablets or capsules varies widely, but is generally expected at approximately age 7 and varies with tablet and capsule size.

Children commonly refuse to take medication if it tastes bad.

The result of lack of adherence can and does lead to hospital admissions for intravenous therapy.
There are many reasons for the dearth of oral pediatric formulations.

Children represent a small proportion of the sick population (the market for these formulations is small).

In addition, the pediatric population as a whole (0–17 years) is heterogeneous, with differing formulation requirements depending on the age and developmental and clinical state of the patient.

Age groups within the pediatric population:
- Preterm newborn infants
- Term newborn infants (0-27 days)
- Infants and toddlers (1 month to 23 months)
- Children (2 – 11 years)
- Adolescents (12 – 16 or 18 years)
• There exists no consistent guidance on dosage form standards for pediatric age, taste preference standards, or acceptable excipients for use in pediatric formulations.

• Finally, there are regulatory issues regarding need for bioequivalence.
• It should be noted that swallowing difficulties are not solely a pediatric issue.

• Other patient subpopulations such as the elderly, or those debilitated by stroke might also benefit from formulations specifically designed for children.
The diversity of physical size and developmental capabilities of the pediatric population drives the need for different formulations, a wide range of dosage strengths within each formulation.

Clinical testing of prototype dosage forms in the pediatric population is limited for ethical reasons, and so, these bioequivalence studies are performed in adults.
Design requirements for oral formulations are primarily based on the patient age, body size, and swallowing capability of the target population.

Establishing the design requirements is generally complicated when the age range of the target population spans from birth to 8 or 10 years of age, as one specific type of dosage form is not ideal to cover this wide age range.
Information exists in the literature and from the European Medicines Agency (EMA) regarding possible acceptable dosage forms for various ages of patients.

For patients below 2 years, liquid dosage forms are widely acceptable.

In some cases, orally disintegrating or film strip-type formulations may also be acceptable.
Between the ages of 2 and 6 years, the ability of a child to swallow a small tablet or capsule is highly variable and many times based on the child's past experience with a particular drug or dosage form.

- A 2011 EMA guideline provides a guide on tablet size for various pediatric age groups (tablets should be no larger than 5 mm for patients less than 6 years of age).

- When patients are over the age of 6 years, there is better acceptance of small to medium tablets intended for swallowing, but there is a significant percentage of the population that still has difficulty swallowing tablets or capsules.
Most children 12 years and older can swallow a tablet or capsule of reasonable size, but what constitutes “reasonable” will vary from patient to patient.

When the age or weight range of the treated population is wide, more flexibility in dosage strengths may be necessary.
- Liquid dosage forms are considered the most flexible in this regard, but liquid formulations carry some important limitations:
  - shaking suspension,
  - transport large multiple-use bottles,
  - accurate measuring device.

- Volume must be taken into consideration:
  - too small, and the dose may be inaccurate
  - too large, and adherence will become problematic.

- Liquids also require preservatives, which may lead to excipient safety concerns.

- One significant liability associated with liquids is the need for taste masking.
Many solid oral dosage forms can have taste problems due to the very bitter taste of the active ingredient.

When solid oral dosage forms are developed, the dosage flexibility is only achieved through the available number of dosage strengths.
Some flexibility in dosage administration can be achieved:

- with granules or multi-particulate dosage forms or
- by tablets that are intended to be orally disintegrating.
• These tablets can also be administered by dispersing the tablet in a liquid prior to administration, but this requires that the caregiver estimates the correct portion of liquid to administer.

• The potential use of this type of administration should be assessed and evaluated for stability and acceptability in patients.
When developing liquid dosage forms, the solubility and stability of the API are critical to designing an appropriate drug product.

The API should be stable enough to allow for at least 18 months of shelf life for the intended commercial product.

For APIs with high aqueous solubility and acceptable stability, it is generally easier to design a liquid dosage form as a solution that will have good dose uniformity.
Special techniques are needed to develop liquid solutions with low aqueous solubility drugs.

With low aqueous solubility APIs taste issues may be reduced, but the challenge of dose uniformity when formulated as suspension increases significantly.

Careful formulation development is required to ensure a suspension that can be accurately dosed with a reasonable amount of mixing.
• It is seldom practical or desirable to perform relative bioavailability studies in pediatric subjects.

• The initial prototype dosage form that is developed must be studied in adults in order to understand the in vivo performance.
- This is the general position of most regulatory agencies, although the US FDA does offer a potential exception for drugs that are classified as Biopharmaceutics Classification System (BCS) Class I.

- Recently, there has been discussion of whether the extrapolation of BCS data from adults to pediatric populations is appropriate.
The BCS system is based on a fundamental model of the gastrointestinal tract for the estimation of the extent of absorption, taking into account important physicochemical–physiological parameters such as:

- aqueous solubility,
- intestinal permeability,
- drug dose,
- volume of luminal fluid contents,
- fluid flow rate, and
- intestinal surface area.
Pediatric developmental changes must be taken into account, as they also play a key role in pharmacokinetics. For example, obvious maturation changes are related to the volume increase of luminal fluids, intestinal surface area, and intestinal permeability.

Administered dose is also fundamentally important, and therefore, there may be a need for a more quantitative, dose-dependent approach to pediatric BCS. Many active compounds in current development have low solubility and permeability and so require excipients to improve oral absorption.
Wu and Benet have proposed an alternative Biopharmaceutics Drug Disposition Classification System which includes the role of metabolism in classifying drugs.
Since the adoption of pediatric regulations in the USA and EU, there is a greater demand for age-appropriate medicines for children.

Despite this growing demand, pediatric drug formulation science is still at an early stage, as it is:
- complex,
- multiparametric, and
- resource and time intensive.
• As discussed previously, tablets and capsules cannot be swallowed by the very young, while liquid formulations may present multiple portability, stability, and dose accuracy problems.

• Recently, there has been an effort to develop solid pediatric formulations that deliver the appropriate dose in a “user friendly” way.
• As the oral pathway is the most common route of drug administration, this is the area in which the greatest progress has been made.
  • Small-sized dosage forms like mini-tablets, pellets, and sprinkles are preferred solid carriers which may be administered alone or dispersed in food.

• Another approach is to develop orally disintegrating drug formulations which disintegrate within few seconds in the oral cavity.
  • Examples of these innovative dosage forms are oral lyophilisates, orally disintegrating tablets (ODTs), and orally disintegrating films.

• Combining both approaches, small sized dosage forms and orally disintegrating formulations, have led to orally disintegrating mini-tablets that may offer advantages for pediatric treatment over conventional techniques.
Recently, the “pill swallowing cup” has been developed for patients who have difficulty in swallowing tablets.

The cup, which contains the appropriate dose, is filled full with a beverage and then the patient drinks the liquid and drug from the cup.
A modified feeding bottle such as the Medibottle® has been developed, delivering the drug while the baby drinks.

Dose sipping technology has been developed in order to deliver a single dose of small-sized pellets, overcoming swallowing issues.

This technology incorporates small-sized pellets in a straw; when the child holds the straw in a beverage and sips, the drug is delivered in a user friendly way.
Any development approach must specifically consider:
- the small market for pediatric formulations (relative to adults),
- the frequent necessity of developing more than one formulation,
- consistent guidance around excipient use and taste masking requirements,
- as well as consideration of a more fit-for-purpose bioequivalence strategy.

The mission of pharmaceutical scientists is to study and develop formulations for the correct use of drugs, ....... especially for children.