Pediatric Formulations: Child-Friendly Oral Dosage Forms

Carlo Vecchio
Pharmaceutical Technologies and Development

- 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.

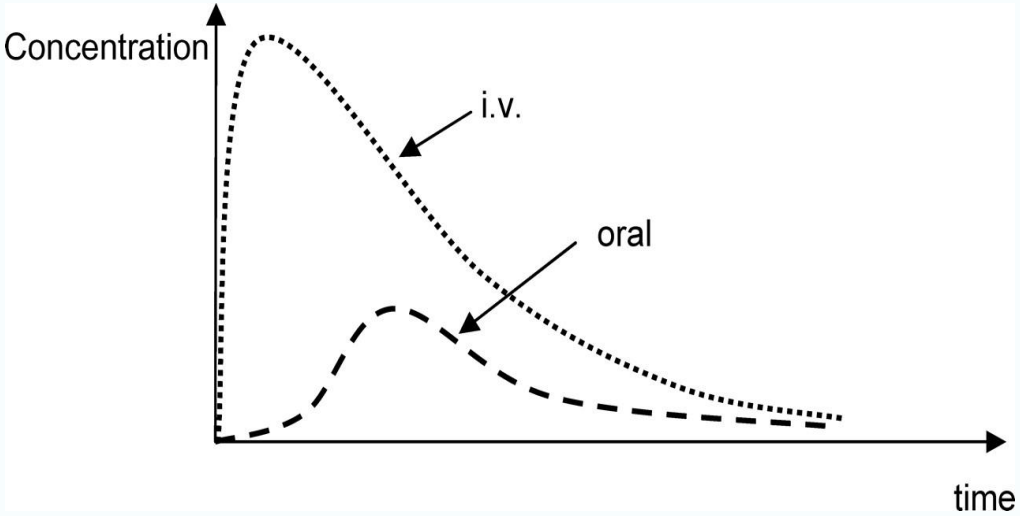
- When developing liquid dosage forms, the solubility and stability of the API are critical to designing an appropriate drug product.

- 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.

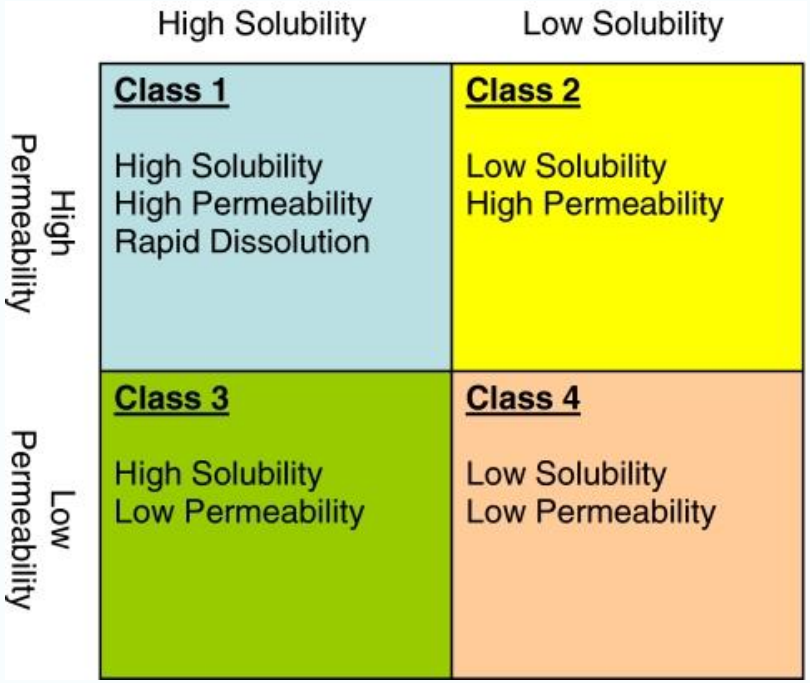
- Special techniques are needed to develop liquid solutions with low aqueous solubility drugs.
- With low aqueous solubility APIs taste issues may be reduced, but the challenge of dose uniformity when formulated as suspension increases significantly.
- Careful formulation development is required to ensure 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.

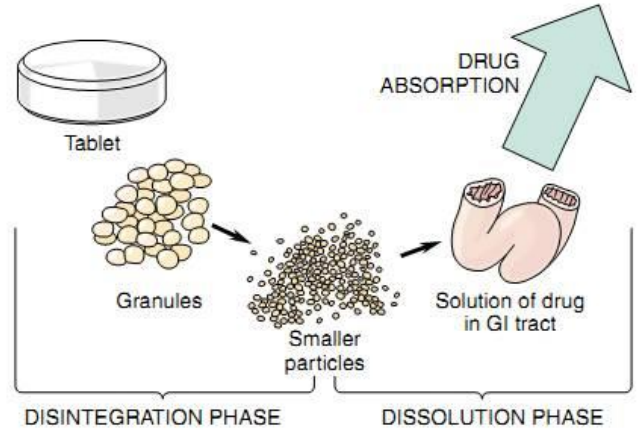
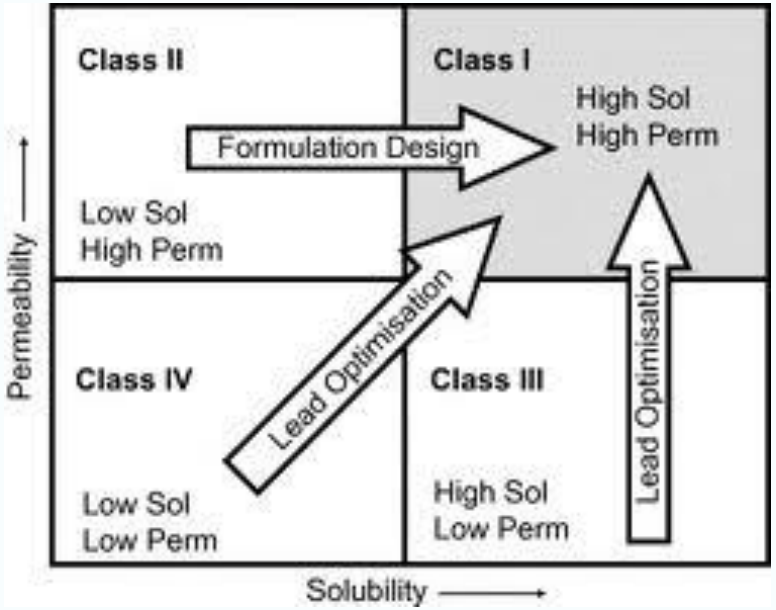


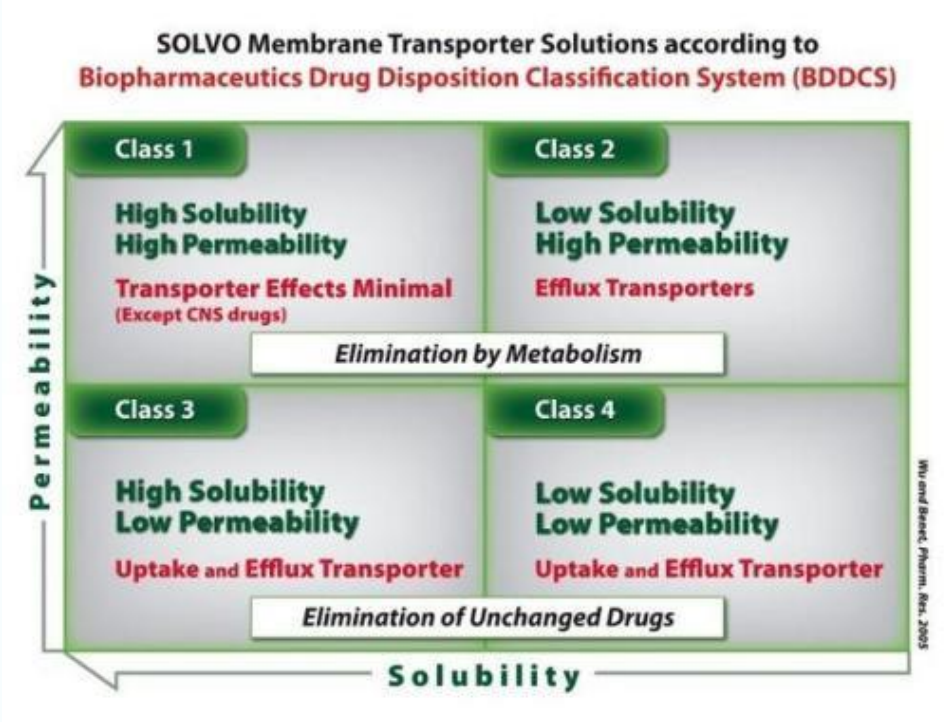
Figure 29-1 Phases of Solid Drug Absorption

- 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.

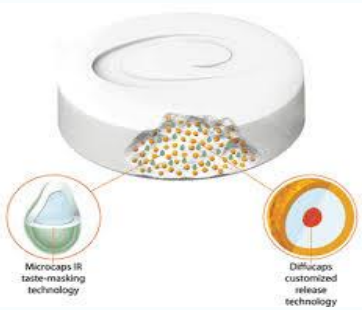


- Since the adoption of pediatric regulations in the USA and EU, there is a greater demand for age-appropriate medicines for children.

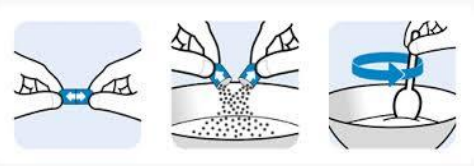
- Despite this growing demand, pediatric drug formulation science is still at an early stage, as it is:
  - complex,
  - multiparametric, and
  - resource and time intensive.

- 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-forpurpose bioequivalence strategy.

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