Advanced Drug Delivery Reviews 190 (2022) 114507

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

Oral drug delivery strategies for development of poorly water soluble drugs in paediatric patient population

Smita Salunke [a,*], Fiona O'Brien [b], David Cheng Thiam Tan [c], David Harris [d], Marie-Christine Math [e], Tina Ariën [f], Sandra Klein [g], Carsten Timpe [h], On behalf of the European Paediatric Formulation Initiative EuPFI

[a] European Paediatric Formulation Initiative (EUPFI), University College London School of Pharmacy, London WC1N 1AX, UK
[b] School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland
[c] AbbVie In, North Chicago, IL 60064, USA
[d] Merck & Co, Inc, Rahway, NJ 07065, USA
[e] Sanofi-aventis R&D 371, rue du Professeur Blayac, 34184 Montpellier Cedex 04, France
[f] Janssen R&D, Turnhoutseweg 30, 2340 Beerse, Belgium
[g] University of Greifswald, Department of Pharmacy, Felix-Hausdorff-Strasse 3, 17489 Greifswald, Germany
[h] F. Hoffmann La Roche AG, Grenzacher Str. 124, CH-4070 Basel, Switzerland

ARTICLE INFO

Article history:
Received 1 March 2022
Revised 14 June 2022
Accepted 17 August 2022
Available online 29 August 2022

Keywords:
Paediatric formulation
Solubility enhancing technologies
Poorly water soluble drugs
Formulation
Lipid based drug delivery
Nanocrystal
Solid dispersion
Cyclodextrin

ABSTRACT

Selecting the appropriate formulation and solubility-enabling technology for poorly water soluble drugs is an essential element in the development of formulations for paediatric patients. Different methodologies and structured strategies are available to select a suitable approach and guide formulation scientists for development of adult formulations. However, there is paucity of available literature for selection of technology and overcoming the challenges in paediatric formulation development. The need for flexible dosing, and the limited knowledge of the safety of many formulation excipients in paediatric subjects, impose significant constraints and in some instances require adaptation of the approaches taken to formulating these drugs for the adult population. Selection of the best drug delivery system for paediatrics requires an efficient, systematic approach that considers a drug's physical and chemical properties and the targeted patient population's requirements. This review is a step towards development of a strategy for the design of solubility enhancing paediatric formulations of highly insoluble drugs. The aim of this review is to provide an overview of different approaches and strategies to consider in order to assist development of paediatric formulation for poorly water-soluble drugs with the provision of examples of some marketed products. In addition, it provides recommendations to overcome the range of challenges posed by these strategies and adaptations of the adult approach/product presentation required to enable paediatric drug development and administration.

Contents

* Corresponding author.
E-mail addresses: s.salunke@ucl.ac.uk (S. Salunke), fionaobrien@rcsi.ie (F. O'Brien), cheng.tan@abbvie.com (D. Cheng Thiam Tan), david.harris@merck.com (D. Harris), marie-christine.math@sanofi.com (M.-C. Math), tarien@its.jnj.com (T. Ariën), sandra.klein@uni-greifswald.de (S. Klein), carsten.timpe@roche.com (C. Timpe).

https://doi.org/10.1016/j.addr.2022.114507
0169-409X/

1. Introduction

The implementation of paediatric specific regulations by the United States (US) Food and Drug Administration (FDA) and the European Medicine Agency (EMA), has steered the development of age-appropriate formulations for children [1]. These formulations include multiparticulates, minitablets and flexible solid oral forms, recommended by the World Health Organization (WHO) as the optimum oral formulations for children's medicines [2]. Challenges in developing oral solid dosage forms for children are multiple, including addressing formulation challenges related to need for dose flexibility, excipient safety, unpleasant taste, and poor solubility of the Active Pharmaceutical Ingredient (API). Since the dissolution of the API in the gastrointestinal lumen is an essential prerequisite for drug absorption, poor solubility can significantly affect oral bioavailability. About 40 % of drugs on the market and nearly 80 % of molecules in the discovery pipeline have low solubility and, as a result, improving solubility is the subject of continued focus within the bio/pharma drug development sector [3,4]. Poor aqueous solubility provides challenges, but also opportunities to scientists working in formulation development.

Poorly water-soluble drugs (PWSDs) can be broadly classified as either, "brick dust" (compounds with limited aqueous solubility due to their tight crystal lattice and high melting point), or "grease balls" (compounds with limited aqueous solubility due to their high affinity for the lipid phase, high logP but with much lower melting point) [5,6]. These compounds present with limited-to-no oral bioavailability which tremendously limits their value and use. Some early terminations of projects in new drug development have been attributed to the poor water solubility of the drug [7]. Sufficient solubility, coupled with appropriate partition coefficient, is a critical requirement in the development of solid oral dosage forms in order to achieve a therapeutic drug concentration in the systemic circulation [8]. For any drug to be absorbed into the systemic circulation, it must be present in solution at the site of absorption. Poor solubility results in incomplete or variable absorption, higher impact of pH and food on drug absorption, and, consequently, poorly controlled pharmacokinetics. This can present major challenges to the successful development of New Chemical Entities (NCEs) including:

- Translating preclinical efficacy
- Inter & intra subject variability
- Poor patient compliance due to higher pill burden
- Food effects
- Difficulty establishing maximum tolerated dose (MTD)
- Challenges for high drug load product design
- Limited portfolio of suitable excipients
- Prediction of amorphous stability
- Need for non-conventional technologies
- Limited manufacturing technologies

Appropriate formulation technologies and regulatory guidance are required to advance these theoretically effective therapeutic compounds, through the development pipeline, resulting in acceptable dosage forms for patients. While determining a formulation approach that provides a safe dose-exposure relationship is still a challenge in developing adult formulations, it is even more difficult in the development of paediatric formulations, due to formulation challenges such need for dose flexibility and patient acceptability. In addition, the impact of ontogeny on drug and excipient disposition across the paediatric age range from new born to adolescents is not yet well understood [9–13].

The guidance documents published by EMA for paediatric drug development are often used during submission of marketing authorisation applications (MAAs) or applications to extend or vary marketing authorisations to the paediatric population (MAVs) and guide paediatric drug development in pharmaceutical industry [1]. However, despite significant regulatory progresses in paediatric drug development, limited information is available on the drug delivery strategies for poorly water-soluble drugs for paediatric patients. The challenges of formulating poorly soluble drugs for children have been documented since the 1930 s, when the attempts were made to prepare liquid preparation of sulfanilamide for children [14]. Sulfanilamide is poorly water soluble and was formulated with diethylene glycol to enhance its solubility. This deadly concoction resulted in diethylene glycol poisoning involving 107 people, mostly children. This is an example that highlights the need to consider the physiological difference between paediatric and adult patients in addition to the physicochemical properties of the drug substance. The challenge to enhance the bioavailability of poorly soluble drugs was also observed in the development of Norvir® (Ritonavir) where early formulation development with surfactants, acids, and other wetting agents did not increase the bioavailability to beyond ~ 4 %[15].

The aim of this review is to provide an overview of different approaches and strategies used in the development of paediatric formulations for poorly water-soluble drugs, including examples of some marketed products.

2. Solubility classification challenges

The growing number of small molecules with increased molecular weights and low aqueous solubilities required the development of adequate formulation strategies and has, over time, led to a much better understanding in the successful strategies used in their formulation [16]. Over the past few decades, various for-

mulation and processing technologies have been developed for these APIs. Guidance is certainly needed on how to proceed strategically, and a starting point is usually the Biopharmaceutical Classification System (BCS). The BCS introduced by Gordon Amidon and co-workers in 1995, has helped to better categorise new drugs according to their aqueous solubility and permeability, with BCS classes II and IV containing the poorly soluble candidates with high or low permeability, respectively [17]. More recently, Butler and Dressman [18] proposed the Developability Classification System (DCS), a modification of the BCS, setting the primary focus on the "developability" of a drug. In contrast to the BCS, it examines the total dose instead of the highest strength in terms of solubility. It allows for assessment of the formulation strategies which can be employed to optimise oral bioavailability; particularly by comparison with formulations utilised by reference marketed compounds in the same DCS-space [19].

Classification of compounds according to the BCS and DCS systems could require a class change for poorly soluble compounds if applied to paediatric applications. The key parameters that define the solubility classification of a drug, i.e., its solubility, highest dose and the volume of the contents in the upper gastrointestinal (GI) lumen, vary between adults and children, and among different paediatric groups, and may change the solubility classification [20].

Children's idiosyncrasies and physiological differences from adults, justify the need for a specific paediatric Biopharmaceutics Classification System (pBCS), preferably by age group [21,22]. Particularly for compounds with poor aqueous solubility, the establishment of paediatric BCS could contribute to the:

- Development of age-appropriate formulations for the paediatric population.
- Assessment of the risk of the inadequacy of an adult formulation to paediatric formulation.
- Development of risk-assessment tools to support development of age-appropriate oral medicines.
- Identification of the risks associated with extemporaneous formulation, as low solubility drugs would be particularly sensitive to formulation differences.
- Formulation bridging, line extensions and minimisation of clinical trial and regulatory burden.

Overall, the development and validation of a pBCS, could improve and facilitate paediatric drug product development. However, current literature indicates that this classification system endeavour is more complicated than an adult BCS, due to the complexity of paediatric groups. The challenges associated with pBCS criteria establishment and the possible approaches for setting the classification criteria are still under investigation [23]. Significant knowledge gaps concerning absorption processes, maturation and growth of the GI tract, impede the establishment of solid, evidence-based pBCS criteria [24]. To explore how many drugs could potentially present challenges in some paediatric groups, del Moral-Sanchez et al. recently attempted creation of a provisional pBCS of the oral drugs included in the Essential Medicines List (EML) for Children by the WHO, and compared the results with the BCS for adults [25,26]. Overall, 24.5 % of the 143 drugs evaluated in the study moved from a favourable class in the BCS into an unfavourable class (i.e., from high to low solubility), in the proposed pBCS. This indicates that due to changes in the limiting factors for absorption, APIs with a well-characterised in vivo performance in adults might perform differently in paediatric patients. The authors recommended the development of a validated pBCS to improve the safety of paediatric therapeutics [23,27,28]. Shawahna investigated the effects of variable age based gastric volume on the BCS solubility class of oral drugs, particularly those available on the WHO's EML for children [21]. The study emphasised that assigning BCS solubility classes in paediatric populations, needs to consider heterogeneity among paediatric populations, as the gastric volume varies with age and body size. The solubility class is assigned based on the solubility of the drug in a volume equivalent to the gastric volume and, therefore, inconsistencies regarding the solubility class can arise when considering paediatric populations as a homogenous group instead of using age-appropriate gastric volume values. Development of a definitive pBCS requires full and thorough understanding of the GI physiology and intestinal permeability in paediatric populations. Age-based changes in the GI fluid composition, volume, and pH are critical for the prediction of age-based solubilities [21]. Further cross-disciplinary discussion, research and knowledge, is required to underpin the development of a suitable pBCS, which would serve as a framework in the development of formulations for the paediatric population.

3. Industrial challenges in selecting enabling technologies for oral drug delivery for the paediatric population

The aim of poorly water-soluble drug delivery techniques is to enhance the solubility of drugs and includes the physical and chemical modifications of drug. Conventional approaches to increase the kinetic or thermodynamic solubility of an API include: (i) micromilling/micronisation, (ii) prodrug, (iii) pH modification (iv) salt formation and (v) addition of surfactants and co-solvents (Fig. 1). While these conventional approaches are simple and applied frequently, their development is challenging when designing a medium to high drug load formulation. For these formulations, enabling technologies such as solid dispersions [29,30,31,32], nanomilling, lipid-based self-emulsifying drug delivery systems [33–35] and cyclodextrin systems [36] are valuable techniques.

Selecting the appropriate technology or strategy to develop formulations requires substantial in-house expertise and specific methodological capabilities. Several review articles outlining strategies useful in the selection of suitable formulation approaches for adult formulations, have been published [37–40]. However, there is a paucity of available literature in case of selection of technology for paediatric formulations. Increased research efforts are required to develop age-appropriate, paediatric focused, versatile drug delivery systems for poorly water-soluble entities.

One of the key considerations in developing suitable products for children and adolescents is the selection of proper dosage forms based on the target population age. Unlike adults, the paediatric population is highly heterogenous and exhibits significant differences in body weight, hence the need to enable flexible dosing. Formulation strategies in early-stage drug development depend significantly on the complexity of the molecule and its physicochemical properties, dosage form, formulation considerations and biopharmaceutical attributes as summarized in Fig. 2 and elaborated in section 3.1 below.

3.1. Dosage form and formulation considerations

Paediatric dosage forms present particular complexity due to the diverse patient population, compliance challenges, dosage form acceptability and safety consideration amongst this vulnerable patient group. The design and selection of age-appropriate dosage forms for the paediatric population, involves the careful consideration and balance between quality target product profile versus technical challenges and development feasibility [41]. Whilst liquids have been the most commonly used dosage form in children due to swallowability and dose flexibility, they are associated with several disadvantages, such as chemical, physical, or microbial

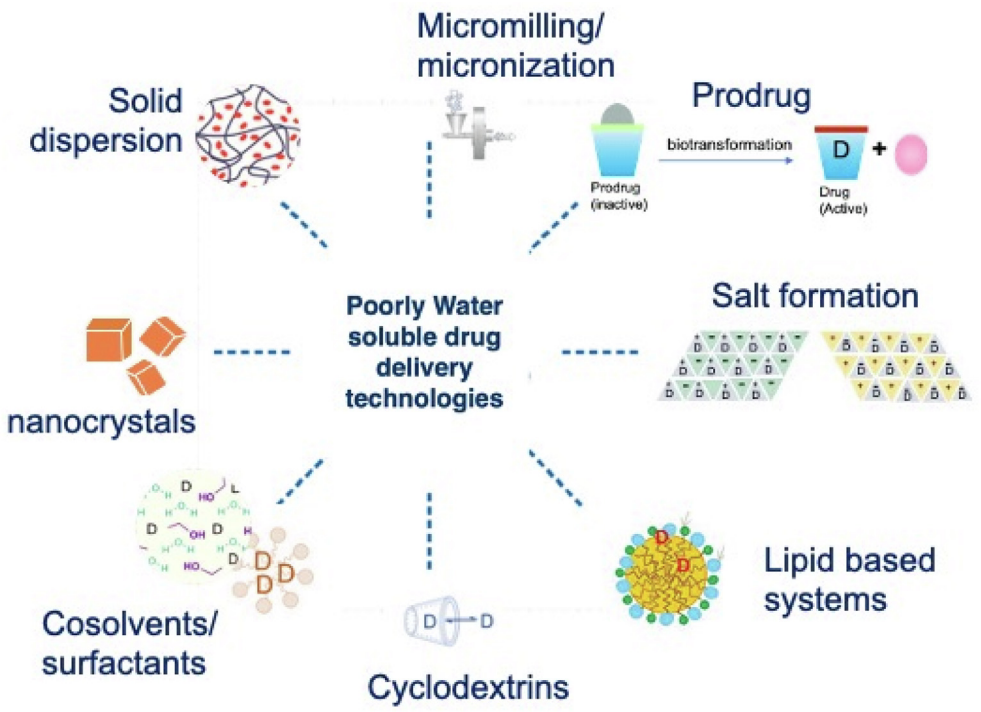

Fig. 1. Commonly used poorly water-soluble drug delivery technologies.

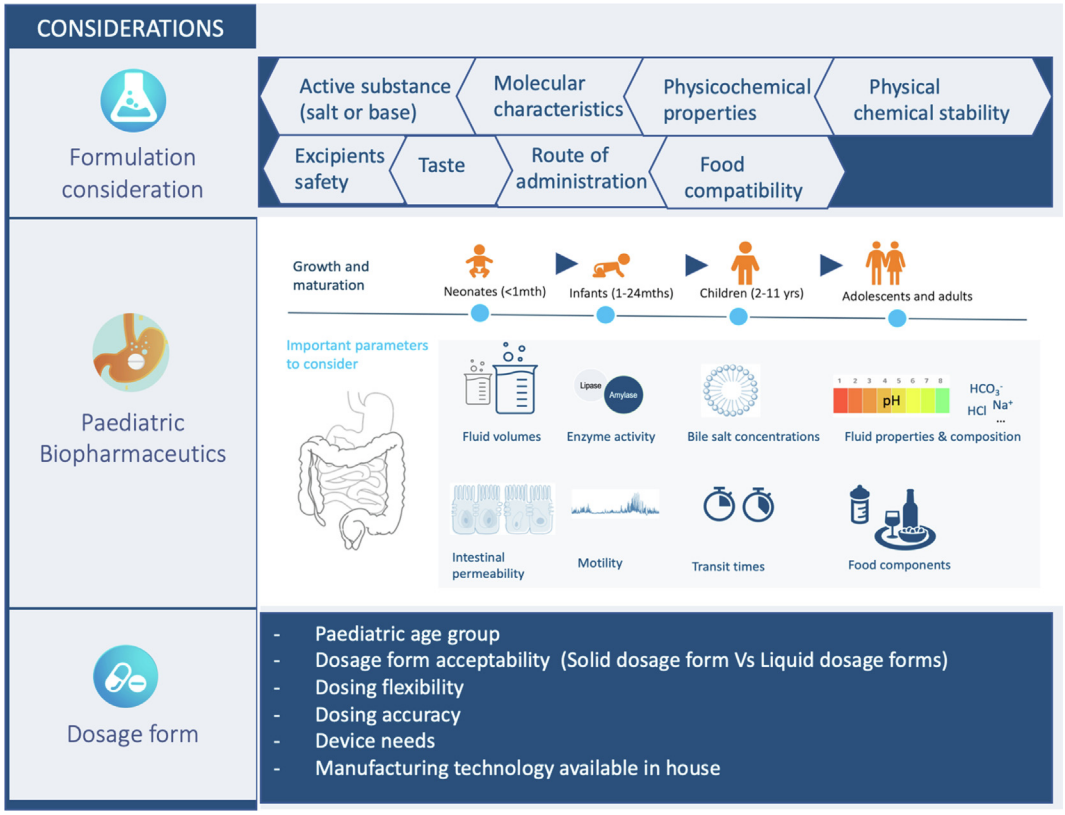

Fig. 2. Considerations for development of paediatric formulations.

instability (requiring a preservative), taste challenges (requiring taste masking), lack of controlled release properties, difficultly to adequately solubilise poorly soluble drugs in acceptable vehicles at adequate concentrations, safety of excipients, and potential dose measurement errors. Hence, there has been a push towards designing oral solid dosage forms using appropriate drug delivery technologies that are age-appropriate and enable dose flexibility, while addressing the limitations listed above[42–45]. These dosage

forms must be able to be manufactured both on a large scale, or extemporaneously on a small scale in hospital pharmacies, dispensaries and within nurse clinics [46]. Orally disintegrating minitablets have been reported as a novel solid drug delivery system suitable for use in paediatric patients, as they enable ease of administration, flexible (individual) dosing to suit a wide age and capability range, they generally exhibit good stability, and have acceptable manufacturing and distribution costs [47–50].

In addition to dosage form considerations (drug layering of pellets or minitablets, and fast dissolving orally disintegrating tablets (ODTs) for paediatric populations), the API salts and excipients need to be carefully evaluated during paediatric pharmaceutical development [51]. The API salts should be selected to assure an acceptable bioperformance considering the physiological developmental stage of paediatric patient [52]. As an example, the solubility of API in liquid dosage forms should be enhanced to avoid the administration of high dose volume. For excipients, the appropriate selection and risk assessment of excipients in accordance with the safety profile in children, tolerability, acceptable daily intake, regulatory status, target age group, the patient's susceptibility, dosage regimen and exposure are required [1]. Understanding how a drug's solubility affects taste is an important factor to consider for paediatric population. The solubility of the drug needs to be balanced with taste-masking, as highly soluble drugs may activate taste receptors on the tongue if they dissolve in saliva within the oral cavity [53]. Food and drinks are commonly used vehicles to facilitate administration of paediatric medicines to improve palatability and enhance patient compliance. However, the physicochemical properties and macronutrient composition of these vehicles may affect the solubility of the drugs. The vehicle-dependent impact on drug solubility could compromise its bioavailability, and ultimately affect the safety and/or efficacy of the drug. This should be taken into consideration during paediatric product development [54].

The diversity of the paediatric age group, particular taste preferences, anatomical and physiological differences between children and adults, ethical challenges in clinical studies and challenges in producing stable and therapeutically effective dosage formulation, present complexity in pharmaceutical development. Adding to this complexity, many of the new generation of small molecule drugs have higher molecular weights, and either high lipophilicity or high melting points. These new, complex molecules not only pose biopharmaceutical challenges, such as poor water solubility and bioavailability, but may also cause manufacturing challenges. Formulation strategies in early-stage drug development depend significantly on the complexity of the molecule and its physicochemical and biopharmaceutical attributes. Hence, before selecting a formulation strategy, one needs to have a thorough knowledge of the physicochemical properties and biological attributes of the drug substance, in particular its solubility and intestinal permeability characteristics. Developing a formulation with optimal bioperformance requires an understanding of molecular characteristics and physicochemical properties which contribute to the poor solubility of various drugs, in order to assure sufficient permeation through the wall of the gastrointestinal tract. These properties include their complex structure, size, high molecular weight, high lipophilicity, compound H-bonding to solvent, intramolecular H-bonding, intermolecular H-bonding (crystal packing), crystallinity, polymorphic forms, ionic charge status, pH, solubility profile, and ability to generate a suitable salt form. For instance, for molecules exhibiting polymorphism, it is important to understand the different polymorphic forms, their stability and properties, and potential to convert from one form to another. The formulation strategy would then be based on preventing the conversion of the selected polymorph and ensuring its stability throughout the clinical stability or shelf life of the product. In addition, the formulator needs information about the potency of the compound, the age of the target population, and the desired route of administration in order to determine the type of final dosage form as well as the required drug load. Knowing what dose is to be administered is also important in the selection of the most appropriate formulation strategy for the compound. The range of doses required throughout childhood can vary. If a medicinal product is to be used in all age groups, theoretically, a range of dose strengths or concentrations should be available to allow simple, accurate and safe dosing [55]. A formulation strategy suitable for a particular dose range (e.g., 5–50 mg) is unlikely to be appropriate for another dose range (e.g.,100 – 1000 mg) and vice versa. Extensive preformulation studies and determination of BCS/DCS classification will help to plan and prioritise the technologies and formulations to consider. For instance, a high melting point compound would exhibit limited practical solubility in a lipid vehicle unless the dose strength is low.

Computational methods that use molecular modelling, dose prediction and solubility parameters are helpful. Physiochemical properties provide the basis for a preclinical risk assessment when evaluating enabling technologies. Selection of appropriate delivery techniques based on practical considerations and in-house expertise should be a part of the strategy. There is no 'one-size-fits-all' approach that solves all the formulation considerations. The success of the formulation will be dependent on the formulators' understanding of the interplay between the physicochemical properties of the drug, the special aspects of the various formulation options and the required in vivo performance. Each technology has its own advantages and disadvantages and cannot be used as universal formulation techniques for all the poorly soluble compounds for paediatric formulation development, especially those which are insoluble in both aqueous as well as non-aqueous solvents.

3.2. Biopharmaceutical considerations

Drug absorption after oral dosage form administration depends on various factors, including the solubility of the API across the gastrointestinal pH range, its stability in the contents of the GI lumen, its permeability across the intestinal epithelium, and its availability at the site of absorption which is affected by GI transit and dissolution/drug release rate [56–58]. Poor oral bioavailability can be the consequence of a complex interplay of various factors of which solubility in the GI lumen is an essential prerequisite. Therefore, when the aim is to translate a poorly soluble drug into a viable paediatric medicinal product, it is essential to ensure a fast and complete dissolution of the maximum administered dose in the target patient group. For adults, various formulation approaches have been developed for successful oral delivery of poorly water-soluble drugs [59] and the use of biopharmaceutical tools was integral in the design and development of many drug products. However, to date no systematic formulation strategies towards paediatric formulations have been reported. From a biopharmaceutical standpoint this is most likely the result of the unknown risk of extrapolating adult methodology into a paediatric population [60]. Children represent a heterogeneous group of patients that grow and mature from prematurity to adolescence. Their growth and maturation results in a continuous change in GI physiology including intraluminal fluid volume and composition and GI transit time [61].

A major challenge for a successful formulation development for poorly soluble APIs, is the assurance of dissolution of the administered dose in the GI environment of the individual patient. In adult formulation development, this target involves dissolving the maximum single dose in the luminal contents of an average adult, after administration with a glass of water in the fasted state. Development of paediatric formulations of poorly soluble APIs is very dif-

ferent, since both the required dose and the GI physiology of children continuously changes and the model of an "average child" cannot be used. Moreover, the volume of co-administered fluid will also be subject to age. Consequently, the in vivo performance of poorly soluble drugs and their formulations are unlikely to be correctly predicted by extrapolation from adult in vivo data or from biorelevant in vitro studies addressing typical dosing conditions in adults. This theory is supported by results of Maharaj et al., who assessed the impact of age-specific changes in GI fluid parameters on the solubility of seven BCS class II compounds [62], and concluded that developmental changes in GI fluid composition can result in relevant discrepancies in luminal compound solubility between children and adults. This was an important step in highlighting the importance of properly addressing intraluminal conditions in the target patient group in in vitro studies, and confirmed that paediatric biopharmaceutics is crucial in the optimisation of the design and development of age-appropriate oral medicines containing poorly soluble drugs. Unfortunately, for several age groups, data required in the assessment of the impact of age on the in vivo solubility of a poorly soluble API, is lacking. This is particularly true for small intestinal characteristics such as pH variations, transit time and bile salt concentrations. Bile secretion in the first 2–3 weeks of life is known to be poor with luminal concentrations lower than in adult intestines (2–4 mM vs 3–5 mM respectively). It is known that drug solubility increases with bile salt concentration and therefore a difference in concentration may have an impact on absorption in younger patients [9]. This is a particular risk for poorly soluble drugs (e.g., hydrocortisone). Major knowledge gaps were identified in the most vulnerable groups of neonates and infants under 6 months of age [63,64]. This is also the patient group most different to adults, and where predictivity from adult parameters is least. Greater access to existing paediatric clinical data would be useful in the validation of new predictive in vitro tools for children of all age categories. As long as these do not exist, it will be important to i) make use of all data already available and ii) to develop systematic approaches for mimicking "worst" and "best case" in vivo scenarios after administration of the API of interest. Such procedure would require detailed knowledge of the API properties, particularly the pKa and the lipophilicity, for determining critical variables (pH, bile salt concentration) of the in vitro test design. Finally, when aiming to address in vivo conditions in newborns (a patient group potentially unlikely to be in fasted condition), fed state dosing conditions (breast milk/-formula milk) might be added to the in vitro test design [65]. If a formulation proves to be robust in both worst- and best-case scenarios, it is likely to show the same for in vivo performance.

In the absence of the predictive tools described above, the approach followed today to develop paediatric formulations of adult therapies is to first predict the paediatric pharmacokinetics of the molecule and to then study the drug in small cohorts of progressively-younger patients, refining the model and updating the pharmacokinetic predictions between each age cohort. This approach minimises the extrapolations which need to be made, and ensures that the youngest patients, in which the biopharmaceutics is most likely to deviate from the biopharmaceutics in adults, are only exposed to the drug after pharmacokinetic and safety data have been obtained in older children.

4. Principal formulation technologies to address low drug solubility

4.1. Salt formation (if the compound is ionisable)

Salt formation is the simplest and most preferred approach to increase solubility and develop age-appropriate dosage forms, such as liquid formulations for oral and parenteral administration. It is also used to control drug dissolution for various purposes. For example, salts are prepared to decrease the solubility of drug substances used in liquid suspension formulations, specifically developed for paediatric population. Limiting the solubility of drug substance used in liquid suspension helps maintain the stability of the suspension, as well as ensuring consistent solid-state properties such as particle size and polymorph, which may significantly impact the absorption and safety of the drug. Additionally, limiting solubility of highly soluble drugs is often used for taste masking of suspensions, by reducing the solution concentration of drug substances with an unacceptable taste. Taste improvement is often achieved by forming salts with long chain fatty acids such as palmitic acid, stearic acid or by forming less soluble salts with calcium or with saccharin, which can also serve as sweetener. Artificial sweeteners have been reported as salt co-formers to improve the solubility and dissolution rate of several drugs, as illustrated with quinine, haloperidol, mirtazapine, pseudoephedrine, lamivudine, risperidone, sertraline, venlafaxine, zolpidem, amlodipine, and piroxicam [66,67]. Taste masking of lamotrigine was achieved by salt formation with cyclamic acid, a commonly used sweetener, where it increased the aqueous solubility and dissolution rate of lamotrigine[68]. Many marketed products exist which use less soluble salt forms for liquid suspension. For example, Tequin® (gatifloxacin) paediatric formulation was developed by forming crystalline complexes with stearic acid and palmitic acid effectively masking the bitter taste of the API [69]. Another example is the significant use of meglumine ibuprofen salt, which in addition to its taste masking effect, also has high solubility in water permitting liquid preparations with increased therapeutic activity [70]. Thus, stable liquid preparations can be formulated having an ibuprofen content as high as 200 mg/5 ml which provide a dose equal to that of the commercial Advil® tablets containing 200 mg of ibuprofen per tablet. Hence, paediatric formulations containing 100 mg/5 ml could be prepared as well as adult or geriatric formulations containing 200 mg/5 ml.

The physicochemical and biopharmaceutical benefits of salts compared to their corresponding non-ionised forms, have been described already by Monkhouse and co-workers [71]. The major advantage of the method is that it can provide considerable increase of solubility (often by > 3 orders of magnitude) [72] and dissolution rate without the need to chemically modify the drug molecule or to use complex enabling formulations. For stable salt formations to be complete, ionisation must be effectively complete such that a single ionisation state can be achieved. pH max (the pH value at which the maximum solubility of the drug is obtained), is an important parameter of a salt that has to be considered, especially in the context of oral delivery. It governs the conversion of the ionised form to its conjugate free base or free acid and, hence, the precipitation behaviour in the gastrointestinal tract. Typically, it is necessary to have at least 2 pH units difference between the pKas e.g. of the base and the corresponding acid. It is recommended that the selection of the right salt should occur at an early drug development stage [73]. Evaluation of the "drugability" properties of a suitable salt form should, in addition to consideration of solubility and intrinsic dissolution rate, include such selection criteria as bioavailability (e.g., preclinical animal studies), stability (both chemical and physical), manufacturability, hygroscopicity, crystal form (polymorph) and mechanical properties (e.g., Hiestand indices). A rational form selection, based on the evaluation of relevant properties for obtainable solid forms including salts, is essential e.g., to avoid a costly and inefficient processes. Numerous attempts have been made to instil an intelligent design into the salt-selection strategy, taking into consideration key criteria for drug substance solid forms [74–76].

4.1.1. Challenges for formulating poorly water-soluble drugs using salt formation technology for paediatric patient population

Traditional salt-forming screening strategies employed inorganic or small organic counterions. In oral drug delivery, the most commonly used counterions over the past three decades include hydrochloride, maleate, mesylate, and phosphate for basic drugs, and calcium, magnesium, potassium, and sodium for acidic drugs [77]. Selection of appropriate base, salt or a polymorphic form with minimum bitter taste is critical for paediatric formulation design. The general consensus about the tastes of divalent salts is that they are complex. The cation is primarily responsible for the sensory characteristics of inorganic salts with modifying effects of the anion. Lawless et al. [78] examined the taste profiles of calcium chloride, magnesium chloride and magnesium sulfate and characterised the taste of calcium and magnesium salts as primarily bitter taste.

Another important topic during salt selection is the consideration of the toxicological acceptance of the preferred counter ions, especially under the aspects of paediatric acceptance e.g., lithium cations in higher concentrations could cause irreparable kidney damages, formation of maleic acid from the maleate anion has reported to cause renal tubular lesions in dogs, calcium salts affect renal function [79,80]. More recently, safety concerns have been voiced surrounding the use of sulfonic acid counterions (mesylates, besylates, and tosylates) [81]. These counterions are strongly acidic (pKa values between − 1.34 and 0.7;) and consequently are widely used to form salts with weak bases. When methanol is used during crystallisation of mesylate salts, it is known that mutagenic methyl methanesulfonate, (a methyl ester of methanesulfonic acid), can be formed. The antiviral product Viracept®, for example, contains nelfinavir as a mesylate salt. The use of this product was suspended by the EMA in 2007 over concerns that it contained high levels of the sulfonate ester, ethyl methanesulfonate (EMS), which is genotoxic and possibly carcinogenic. However, recent evidence suggests that the high levels of EMS in Viracept® resulted from contamination of the starting material rather than being a side reaction during salt formulation [82]. The use of equimolar concentrations of drug and counterion can eliminate the potential for EMS to form during salt manufacture, and mesylates remain popular as potential counterions. In an attempt to simplify counterion choice based on toxicity, monographs on 68 salt-forming acids and 27 salt-forming bases have been published in the Handbook of Pharmaceutical Salts: Properties, Selection and Use, as well as a comprehensive list of salt-forming acids and bases with information regarding their safety/toxicity [83,84]. Acidic or basic counterions can alter the pH of the microenvironment in liquid dosage forms. In turn, changes in pH can influence the reactivity of an API with excipients, and can lead to either the improved stability or degradation of the API. Thus, the incompatibilities of counter ions with functional groups from NCEs or excipients, should also be considered.

The Route of Administration (ROA) also plays a critical role in the selection and toxicity of counterion. Counterions that are suitable for one ROA may be unacceptable for other ROA, as the PK, bioavailability and biodistribution differs. A list of use of common anionic and cationic counter ions in industry, based on route of administration (including counterions that have significant history in oral formulations and 'generally recognized as safe' (GRAS) status of each counter ion) has been published as a benchmark for current use within USA [85].

Overall, considering the unique attributes of the paediatric population, the safety of the counterion is one of the most important factors in considering the applicability of salt formation as a bioavailability enhancement strategy.

One of the challenges and issues with the application of salts in oral delivery, is their behaviour in biorelevant conditions. If the pH max is not in the range of physiological pH values, precipitation can occur of the corresponding free base or acid form under the pH conditions in different GI tract regions (e.g., transfer of an acidic salt into the duodenum causing precipitation of the corresponding free base with lower solubility). This is usually the case for acidic drugs in the stomach and basic drugs in the intestine. The precipitated form could also reduce the dissolution rate of the salt if precipitation occurs on the surface of the salt. Similarly, the formation of a gel layer on the surface could inhibit the de-aggregation and also dissolution of the salt (e.g., warfarin sodium salt).

The salt form of an active substance may also affect tolerability, e.g., gastrointestinal irritation which may be dependent upon the aqueous solubility and dissolution rate of different salt forms administered by the oral route. Hydrochloride and fumarate acid salts could evoke oesophageal lesions as described for alprenolol HCl vs the corresponding benzoate, maleate and sebacate salts which do not have any irritant effects on the oesophagus [86]. Nitrate salts may be converted into potentially mutagenic *N*-nitrosamines and hence are of safety concern [87]. In the GI tract, nitrate may be converted to nitrite, leading to methemoglobinemia, particularly in children [88]. Nitrate salts may also cause GI tract irritation in some species. These concerns limit the usefulness of this anion in oral formulations. Lauryl sulfates may cause GI irritation at moderate doses. The degree of solubility enhancement might not be sufficient for drugs with extremely poor aqueous solubility (e.g., itraconazole), and the common ion effect would be very pronounced. In these cases, ionic liquids could be prepared [89]. Another option is to combine the salt concept with other solubility enhancement approaches, such as the amorphous solid dispersions.

4.2. Solid dispersion (SD)

Solid dispersions (SDs) are based on a molecular or amorphous dispersion of a drug in a polymeric (crystalline or amorphous) carrier matrix[90]. This approach enhances the solubility of the drug in the physiological media by disrupting the crystal lattice and minimising the crystal lattice energy requirement for dissolution. In the physiological media, dissolution of the solid dispersion forms a thermodynamically *meta*-stable supersaturated state that is stabilised by the polymeric carrier matrix or other excipients. The selection of the polymer carrier matrix and other excipients (e.g., surfactant) is based upon the miscibility of amorphous drug–polymer systems[91]. SDs have gained popularity and are being extensively used as conventional approaches to enhance dissolution and oral absorption of the drug. SD formulation provides the benefit of rapid dissolution of poorly water-soluble drugs while minimising recrystallisation of drug molecules or clusters due to molecular interactions and steric hindrance within the carrier matrices[92]. However, the formulation of SDs also presents challenges, including the miscibility behaviour between drug(s) and carrier polymers, the maintenance of the metastable state after the manufacturing of the formulation, and a lack of adequate models to accurately predict the miscibility and stability of SD [91]. As each poorly soluble drug exhibits unique physicochemical properties which result in a variety of formulation and processing challenges, applying a single SD manufacturing technology is unlikely. Hence, the development of SDs requires adequate manufacturing techniques that can be extended to commercial production such as spray drying and hot melt extrusion (HME) [90].

In HME, the drug substance is extruded with a polymer and a surfactant (if required) at a suitable temperature to dissolve the drug in the molten polymeric carrier matrix [93]. HME is a solvent free process and is conducted using a single or twinscrew extruder [94]. The absence of organic solvent avoids potential solvent related toxicity concerns [95]. HME also offers the opportunity of direct shaping, and is applicable to hygroscopic and moisture-

sensitive drugs [96]. However, HME may not be feasible for thermally-unstable or high-melting-point drugs and may only be able to support a limited drug loading.

Spray drying could be used as an alternative to HME. In spray drying, the drug, polymer, and surfactant (if required) is solubilised in a solvent, and sprayed through a high-pressure or two-fluid nozzle at a temperature above the solvent's boiling point. Spray drying does not apply excessive heat during manufacturing and could therefore be used for a broader range of APIs and polymers [97]. However, spray drying has several disadvantages such as the use of solvents, the small particle size distribution of the resulting SD, difficulties to reproduce particle morphology, and high operating costs.

The SD technology has evolved and many commercial products developed using this technology have been successfully launched in different disease areas, namely, the treatment of HIV infections, transplantation medicine, oncology, and others [98]. An overview of the marketed products approved by the FDA for adults and for children using different manufacturing technologies like HME and spray drying is listed in Table 1.

4.2.1. Challenges of formulating poorly water-soluble drugs using solid dispersion technology for paediatric patient population

Most of the marketed solid dispersion products are available in tablet dosage form. However, the use of tablet can be challenging for paediatric patients especially in younger subset. Children may need smaller dosage forms for ease of swallowability, a different dosing regimen with dosing flexibility, and potential compliance challenges [99]. To mitigate these potential challenges, drug delivery systems and alternative oral dosage forms such as orodispersible tablets, films, granules, pellets, and others were developed. Another example developed by Farkas et al. [100] combined the medicated straws technique and SD formulations. This drug delivery system maintains the stability of the formulation in solid dosage form and converts the solid dosage form into liquid prior to dosing to aid precise dosing and improve compliance. Solid dispersion requires additional excipients such as polymers or surfactants to maintain its metastable state. The additional excipients may introduce higher pill burden and necessitates the administration of a large tablet or multiple small tablets, pellets, or granules. The additional excipients should also meet the regulatory requirements and be suitable for the paediatric patient population. Their respective impurities must be within acceptable level for the paediatric patient population. The use of excipients that are classified as GRAS based on FDA's inactive ingredients database (IID), in paediatric formulations may require additional due diligence. The FDA's IID provides a list of GRAS excipients and their respective acceptable levels, but does not specify the use for paediatric and non-paediatric indications. Thus, a review of the pharmacology, toxicology and preclinical data is critical to ensure the appropriate excipient and level is used.

Moreover, SDs are in a metastable state and have the intrinsic tendency to spontaneously revert to a more stable crystalline state due to both thermodynamic and kinetic driving forces. Polymers used in SDs may potentially absorb moisture and lead to phase separation, loss of amorphous state, and crystal growth, which result in decreased dissolution rate and solubility. Therefore, SDs require careful handling and storage. Since SDs are metastable, the preparation of SD as ready-to-use (RTU) oral suspension is not feasible. Water in the RTU oral suspension may act as a plasticiser to reduce the glass transition temperature of solid dispersion and increase the risk of recrystallisation or may dissolve the SD outright. In addition, the selected surfactant used in the oral suspension may also impact the recrystallisation risk. Chen et al. observed that sodium dodecyl sulfate and polysorbate 80 promote the crystallisation of celecoxib amorphous solid dispersion suspension. In contrast, sodium taurocholate and Triton X100 inhibited the crystallisation[101]. Therefore, recrystallisation tendency evaluation is important if the adult solid dispersion formulation is utilised as paediatric oral suspension. Hence, SDs are often developed as solid dosage forms such as tablets, granules, pellets or dispersible tablets to circumvent the recrystallisation risk of oral suspension and leverage the established adult formulation developed with an enabling technology. It may be feasible to use extemporaneously-prepared suspensions or dispersions of SD in liquids for dosing paediatric patients who are unable to ingest solid formulations, as noted below, but the physical stability (ie, dissolution of the SD and subsequent crystallisation of the API) must be rigorously studied. Due to the various challenges related to the development, formulation, and stability of the final drug product, the number of commercial products based on the SD technique is limited, despite its various advantages. Table 1 presents a list of commercial products for paediatrics that use SD techniques and few are discussed below in light of challenges to paediatric applications.

- Kaletra® (lopinavir/ritonavir)[102] and Norvir® (ritonavir)[103] were developed as SD tablets for adult patient population and oral solution for paediatric patients. Subsequently, Norvir Oral Powder® (NOP) for paediatrics was developed with the intent to replace oral solution to mitigate potential risk associated with ethanol and propylene glycol solvents and to attain longer term shelf life [15]. NOP is manufactured by milling the adult SD extrudate intermediate and filling the resulted powder into stickpacks. The NOP is suspended in liquid vehicles or sprinkled on soft foods prior to administration. Another lopinavir/ritonavir oral pellets in capsule formulation was also developed by Cipla ltd as SD. The oral pellets are sprinkled over sweetened porridge prior to administration to paediatric patients [104].
- Etravirine® solid dispersion tablet may be placed in a glass of water and stirred well to form suspension prior to administration in paediatric patients [105]. The Etravirine® suspension needs to be swallowed immediately to minimise risk of drug recrystallisation (limited extended in-use storage) and requires rinsing to ensure complete dose is administered.
- (Sporanox®) Itraconazole was developed as a hydroxypropyl methyl cellulose (HPMC) based SD formulation spray-dried on sugar beads for the adult patient population[106,107]. Subsequently, a liquid oral solution using hydroxylpropyl-beta-cyclo dextrin as a complex-forming agent was developed for the paediatric indication and approved for use in children above 3 years old. In contrast, Itraconazole (Onmel®) was developed using a HPMC based SD formulation and manufactured by HME without paediatric indication [108].
- Three Posaconazole® (POS) formulations were developed and received marketing approval for use in adults in Europe, including an oral suspension (OS), a gastro-resistant tablet (hereafter referred to as tablet formulation), and a concentrate for solution for infusion (IV) formulation. The POS tablet formulation demonstrated improved oral bioavailability over the OS in adults; however, the current POS oral tablet is too large to be easily swallowed by young children and does not allow for weight-based dosing. Therefore, POS Powder for Suspension (PFS), has been developed which consists of the same extrudate material/intermediate developed for the POS tablet [109].
- Tacrolimus (Prograf®) did not have a suitable paediatric formulation during the initial launch of the adult formulation [110]. Up until 2009, only tacrolimus capsules were available for oral administration and tacrolimus powder was used to prepare oral suspension. Due to the lack of an approved oral formulation suitable for children and for seriously ill adults with difficulties to swallow capsules, there was a widespread off-label clinical

Table 1
Selected marketed products containing solid dispersion.

Drug substance (Trade name, Company)	Indication	Processing technology	Adult formulation	Paediatric formulation	Comments
Lopinavir/Ritonavir (Kaletra®, AbbVie) [102]	HIV infections	Hot melt extrusion	Melt extruded solid dispersion with 200 mg lopinavir/50 mg ritonavir	Oral solution; For children with 10 kg body-weight or more: A down-scaled tablet with 100 mg lopinavir/25 mg ritonavir has been developed.	Oral solution should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days has been attained.
Lopinavir/Ritonavir (Cipla ltd.)	HIV infections	Hot melt extrusion	–	Oral pellets in capsule (40 mg lopinavir/ 10 mg ritonavir)	
Ritonavir (Norvir®, AbbVie)	HIV infections	Hot melt extrusion	Film-coated tablet (100 mg)	Oral solution (80 mg/ml) Oral Powder (100 mg packet)	NORVIR oral solution should not be administered to neonates before a postmenstrual age of 44 weeks has been attained
Etravirine (Intelence®, Janssen-Cilag)	HIV infections	Spray drying	Tablets (100 or 200 mg)	Tablets (25 mg, 100 mg, and 200 mg) – 6 years to less than 18 years of age and weighing at least 16 kg. Tablets may be administered as suspension.	Tablets should be taken orally, following a meal
Itraconazole (Sporanox®, Janssen)	Fungal infections	Spray-drying on sugar beads (HPMC-based)	100 mg Itraconazole capsule	Sporanox oral liquid (10 mg/ml) – HPβCD 40 %	Oral solution and capsule dosage form should not be used interchangeably. Oral solution to be administered on an empty stomach and capsules to be administered with food. The oral liquid should not be used in patients with glomerular filtration rate (GFR) less than 30 ml/min because HPβCD has reduced clearance with renal failure
Posaconazole (Noxafil®, Merck Sharp & Dohme)	Antifungal agent for treatment of Aspergillus and Candida infections)	Hot-melt extrusion with HMPCAS	Gastro (acid) resistant 100 mg tablet Oral suspension 40 mg/mL	Oral suspension; Powder for Suspension (PFS)	The posaconazole oral suspension and delayed-release tablet are approved for patients aged 13 years and older (USA) or adults aged 18 years and older (Europe).An oral suspension is to be prepared from sachets containing powder and (mixing liquid) for oral administration.
Everolimus (Afinitor Disperz®, Zortress®, Novartis) [170]	Tuberous sclerosis complex (TSC) with giant cell astrocytoma (SEGA)	Solvent-based process	Solid dispersion formulation	Tablets (2.5 mg, 5 mg, 7.5 mg, and 10 mg) Dispersible tablets (2 mg, 3 mg, and 5 mg) for oral suspension.	The slightly lower bioavailability of the suspension was acceptable and the suspension in water can be administered in patients unable to swallow tablets as a whole.
Tacrolimus (Prograf®, Astellas Pharma)	Organ transplant	Spray drying	Capsules (0.5 mg, 1 mg and 5 mg)	Tacrolimus granules (0.2 mg sachets)	Granules dispersed in 15–30 ml water; to be administered immediately after preparation. The Prograf Granules are not to be sprinkled on food. Off-label clinical practice to break capsules and use granules
Ivacaftor (Kalydeco®, Vertex) [112,113]	Cystic fibrosis (CF)	Spray drying	Film-coated tablet (150 mg)	Tablets (150 mg) for patients 6 years and older. Oral granules (25 mg, 50 mg and 75 mg packets), cystic fibrosis (CF) in patients age 4 months to less than 6 years old.	The use of Kalydeco in children under the age of 4 months is not recommended. Prepared granules in dosing vehicle is administered within 12 h.
Lumacaftor/Ivacaftor (Orkambi®, Vertex)	Cystic fibrosis (CF)	Spray drying	Film-coated tablet (200 mg lumacaftor and 125 mg Ivacaftor)	Tablets (200 mg lumacaftor and 125 mg Ivacaftor) for people 6 years and older. Oral granules (150 mg lumacaftor and 188 mg ivacaftor packets) for children 2 to less than 6 years.	It is not known if Orkambi is safe and effective in children under 2 years of age.
Rosuvastatin (Crestor®, Astra Zeneca)	Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, hypercholeterolemia	Spray drying	Film-coated tablet (5 mg, 10 mg, 20 mg, 40 mg)	The 40 mg tablet is not suitable for use in paediatric patients. Patients aged 6 to 9 years could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years to a maximum dose of 20 mg once daily according to the individual response and tolerability in paediatric patients	Crestor is not recommended for use in children younger than 6 years.In children 6 to 17 years of age with homozygous familial hypercholesterolaemia. The recommended maximum dose is 20 mg once daily.

practice to break the Prograf® capsules and use the granules. The granules were used for preparation of liquid dispersion, for swallowing or for administration via a (non-polyethylene) nasogastric tube. However, making fine dosage adjustments for small- sized children was cumbersome. Hence, a new oral granule formulation was designed to provide a dosing formulation suitable for paediatric transplant recipients, and to provide a formulation that allows fine dose adjustments. This granule formulation was approved and launched in Japan in 2001. The smallest dose unit for immediate- and prolonged-release cap-

sules is 0.5 mg, tacrolimus granules are available as 0.2 mg sachets that can be suspended in water and administered orally. The 0.2 mg sachet, therefore, allowed for more precise dosing and dose titration than the capsule formulation. It offered an alternative for paediatric patients who are unable or unwilling to take a solid oral dosage form. The granule formulation is based on the composition of the intermediate granules (SD Formulation) used in the manufacture of the marketed immediate release capsule formulation of Prograf® 0.5 mg, 1 mg and 5 mg capsules [111]. Prograf® granules have been previously approved as Modigraf® (tacrolimus) in 29 European countries and in Japan as Prograf® Granules.

- Ivacaftor (Kalydeco®) oral granules used against cystic fibrosis have been developed for age groups between 4 months to under 6 years of age [112,113]. The granules are added to 1 teaspoon of soft food such as yogurt, applesauce, water, milk, or juice in combination with a high fat meal before or after the drug administration. The prepared granules in dosing vehicle are administered within 12 h.

Developing a SD is an effective method to improve the performance of poorly water-soluble drugs. However, a knowledge gap exists for the in vitro and in vivo relationships and is more challenging in the heterogenous paediatric patient population. The development and in vitro evaluation of SDs are performed using bio-relevant and traditional dissolution testing. The SD efforts focus on increasing drug solubility and achieving the "spring-and–parachute" effect. Advances in improving physical stability of SDs, ability to prolong the supersaturation of the drug in GI fluids, and requirement of development of paediatric formulation by legislation is anticipated to advance the development of SD formulations for poorly soluble drugs in the future.

4.3. Lipid-based drug delivery systems (LBDDS)

Lipid-based approaches to drug delivery have been extensively researched and widely used for their ability to enhance oral absorption of BCS Class II or IV molecules, which have a high/low permeability and a low aqueous solubility. Lipid-based drug delivery systems (LBDDS) are well recognised as a frontline formulation technology to address the physicochemical and biological challenges of poorly soluble APIs, particularly those that are relatively lipophilic. They enhance drug solubilisation during GI processing by creating a lipophilic microenvironment that restricts drug precipitation, while concurrently facilitating drug transport towards intestinal absorption sites [114]. LBDDS have the potential to decrease the food-effect and to increase reproducibility of the pharmacokinetic profile of those orally administered drugs by reducing erratic absorption. The list of marketed products that utilised LBDDS for both adult and paediatric formulations is included in Table 2. Additionally, a non-exhaustive list of recently marketed products that utilise LBDDS has been published by many authors [115]. This highlights the breadth of LBDDS application which expands across all BCS Classes and a range of finished dosage forms. However, full commercial adoption of lipid-based formulations for oral bioavailability has still been an uphill battle. They are still rarely approved and brought to market, still being outnumbered 25:1 by more conventional formulations [116], only accounting for around 2–4 % of commercially available drug products surveyed in 3 markets worldwide [115,117]. The pharmaceutical industry has partially been reluctant to embrace lipid drug products and the reasons are multifactorial. The primary reason is that most APIs do not possess the necessary lipid solubility to be formulated as LBDDS. In addition, the range of lipid-based excipients and the abundance of factors required in determining which combinations of lipids, cosolvents, and surfactants to select, how changes in composition affect performance of the formulation, makes LBDDS a complex, formulation-dependent technology. Lipid based systems can be difficult to compress and film coat due to the soft, friable properties of the lipidic excipients. Many lipid-based drug products are liquid in soft-gel capsules. Special technologies are required to fill hard or soft capsules and capsule softening, shell brittleness, and leakage of fill are all possible problems associated with liquid formulation in capsule. Furthermore, the oral administration of liquid lipid can be associated with an unpleasant taste that may be unacceptable to paediatric patients. Low drug solubility in the lipidic excipients may limit the drug loading of the formulation, especially if high doses would clinically be required (e.g., in oncology, HIV treatments). A general target drug solubility limit of 25–50 mg/ml in lipidic excipients has been postulated [118] but because lipid formulations are multicomponent systems and have complex behaviour, it is obviously not easy to predict if a drug is an appropriate candidate for a lipid based formulation with sufficient solubility [115]. PWSDs that have high log P, low melting point and high lipid solubility are ideally suited to lipid-based formulation while low log P and high melting point drugs can be challenging to formulate in lipid-based formulations. The release of hydroperoxides and volatile by-products resulting from the degradation of lipids and oils represent a physicochemical stability risk of lipid formulation and may also result in in vivo toxicity. Generally, formulations in which the drug is partly dissolved and partly suspended in crystalline form should be avoided as this carries the risk of physical instability.

In addition, the investigational tools to correctly classify, characterise, and predict the in vivo performance of the lipid formulations are still lacking. LBDDS comprise a broad range of formulations from simple oil solutions and emulsions, to complex combinations of oils, surfactants, co-surfactants and sometimes co-solvents in addition to active compounds such as micellar systems, self-emulsifying drug delivery systems (SEDDS), and self microemulsifying drug delivery systems (SMEDDS). In order to simplify and group formulations, several classifications and rules have been proposed with respect to composition, content of hydrophilic solvents, dispersion, droplet size, impact of aqueous dilution, digestibility in vivo and miscibility of the system components. Benameur classified the approaches in the design in 2 categories: lipid-based formulations, and lipid carriers as particulate systems (liposomes, solid lipid nanoparticles, lipid implants, lipid microtubules and microcylinders, lipid microbubbles, lipospheres, microspheres, pellets, nanostructure lipid carriers) [119]. Pouton introduced the lipid formulation classification system (LFCS) in 2000 [120] and later updated the classification to expand the formulation groups [121]. The LFCS classifies lipid-based formulations into four main types, based on the relative proportions of included lipids, surfactants and cosolvents. Several authors have since adapted the Pouton classification but there are elements that such a simplified classification cannot cover. Most recently, attention has switched to the classification of lipid-based formulations based on in vitro performance, rather than solely on composition. The Lipid Formulation Classification Scheme Consortium generated a large database describing the behaviour of Type I-IV formulations and used these data to create lipid formulation—performance classification system (LF-PCS) that grades lipid-based formulations based on in vitro performance in dispersion and digestion tests [122].

Looking at these different types of lipidic systems under the aspect of paediatric drug delivery, the "landscape" of marketed lipid products seems to be quite diverse and rather complex. It is probably difficult to define clear rules for the different drugs, required dosage strengths and type of systems. In a few cases, it is obvious that pharmaceutical companies have developed alternative liquid dosage forms or solid forms to cover paediatric needs.

Table 2
Selected marketed products containing lipid-based systems.

Drug substance (Trade name, Company)	Indication	Formulation type	Adult formulation	Paediatric formulation	Comments
Valproic acid (VPA)	Complex partial seizures (epilepsy	Type I LBDDS (Oils without surfactants (eg. tri-, di-, and monoglycerides)	Soft gelatin capsule (500 mg)	VPA syrup	Substantial pharmacokinetic (absorption) differences found between different formulations
Tipranavir (Aptivus®, Boehringer Ingelheim)	HIV antiviral	Adult formulation: Type III LBDDS (Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients) Pediatric formulation: Type IV LBDDS (Water-soluble surfactants and co-solvents (no oils)	Soft gelatin capsule (250 mg) 100.0 mg ethanol, 455.0 mg macrogolglycerol ricinoleate and 12.6 mg sorbitol, mono/diglycerides of caprylic/capric acid, propylene glycol,	Oral solution (100 mg/mL) Polyethylene glycol 400, vitamin E polyethylene glycol succinate, purified water, and propylene glycol	Safety and effectiveness have not been established in pediatric patients less than 2 years of age. The available clinical data do not support the use of Aptivus oral solution in adolescents or adults. Compared to the capsules, tipranavir exposure is higher when administering the same dose as oral solution. Also, the composition of the oral solution is different from that of the capsules, with the high vitamin E content. Both of these factors may contribute to an increased risk of adverse reactions. Therefore, patients should not be switched from Aptivus capsules to Aptivus oral solution. Benefits outweigh the risks of Aptivus oral solution only in children between 2 and 12 years of age without any other therapeutic option. The exact dose should be measured using the supplied measuring syringe and adapter.
Amprenavir (Agenerase®, GSK)	HIV antiviral	Type IV LBDDS (Water-soluble surfactants and co-solvents (no oils);	Soft gelatin capsule (50, 150 mg) 23 % D-alpha tocopheryl polyethylene glycol 1000 succinate 60 % polyethylene glycol 400 (PEG 400), and 5 % propylene glycol	Oral solution (15 mg/ml) 12 % TPGS, ~17 % PEG 400 and ~55 % propylene glycol and flavored with grape, bubblegum and peppermint.	Agenerase® Capsules and Agenerase® Oral Solution are not interchangeable on a milligram per milligram basis. Agenerase® Oral Solution is contraindicated in infants and children below the age of 4 years and recommended to be used only when Agenerase® Capsules or other protease inhibitor formulations are not therapeutic options. European Commission issued a decision to withdraw the marketing authorisation for Agenerase® in 2010. It is also withdrawn in US.
Cyclosporin A (Neoral®, Novartis)	Immunosuppressant	Adult: Type IIIA LBDDS; fine emulsion - Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients) Paediatric: Type IIIB LBDDS microemulsion - Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	Soft gelatin capsules 25 mg, 100 mg; Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-α-tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine, and other	Oral solution (100 mg/ml) −11.9 % ethanol, dl-α-tocopherol, corn oil-mono-ditriglycerides, cremophor RH 40, and propylene glycol.	Limited PK data in pediatric populations. Neoral Oral Solution should be diluted, preferably with orange or apple juice. Neoral contains around 12 % vol. ethanol and should be taken into account when prescribing it in paediatric patients.

(*continued on next page*)

Table 2 (*continued*)

Drug substance (Trade name, Company)	Indication	Formulation type	Adult formulation	Paediatric formulation	Comments
Sirolimus (Rapamune®, Pfizer)	mTOR kinase inhibitor	Type III LBDDS (Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients) Tablets – Sirolimus incorporated in a NanoCrystal Colloidal Dispersion (Nanodispersion)	Oral solution (1 mg/ml) phosphatidylcholine, mono- and di-glycerides, soy fatty acids, ascorbyl palmitate, polysorbate 80, ethanol, and propylene glycol. Nanoparticulate tablet (RAPAMUNE® 1 mg and 2 mg tablets)	Oral solution (1 mg/ml)	Oral solution contains up to 3.17 vol% ethanol (alcohol), which can be potentially harmful for children. Also, it contains polysorbate-80, which is known to increase the rate of di- (2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of oral solution. Taste, and the requirement for refrigerator storage, protection from light, and disposal of the oral syringe after a single use makes the oily solution an inconvenient dosage form The safety and efficacy of Rapamune in paediatric patients below the age of 13 years have not been established.
Efavirenz/Sustiva® oral solution /Bristol-Meyers Squibb	HIV antiviral	Paediatric: Type IIIB LBDDS microemulsion - Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	Hard gelatin capsules (50 mg, 100 mg, 200 mg)	Oral solution (30 mg/ml) in medium chain trigycerides (MCT) in combination with benzoic acid and strawberry/min flavour.	Dose for adults 600 mg (upto 20 ml); Pediatrics 270–600 mg (9–20 ml); The dosing regimens deliver maximum amount of MCT per unit dose of any currently marketed oral lipid based formulation. The safety and efficacy of efavirenz in children below the age of 3 months or weighing less than 3.5 kg have not been established. A concern is raised with regard to the compliance (poor palatability and/or with dosing accuracy) with the oral solution formulation. Hence, the oral solution is reserved to those unable to swallow the solid formulations. For patients at least 3 months old and weighing at least 3.5 kg who cannot swallow capsules, the capsule contents can be administered with a small amount (1–2 teaspoons) of food using the capsule sprinkle method of administration.

Examples of selected commercialised lipid-based formulations for adults and paediatric as per the classification is summarised below.

4.3.1. Lipid classification type i formulations (Oils without surfactants (e.g. tri-, di-, and monoglycerides))

It is evident from the literature and recent studies that the big solid dosage forms such as capsules, soft gelatin capsules, tablets are not suitable and unacceptable for patients that are unable to swallow. Oral solutions are common dosage forms for children. While the majority of them are aqueous based, few are lipid-based or contain a significant amount of a lipid as a critical formulation component. The simplest lipid-based formulations contain only one excipient such as oleic acid, corn oil, peanut oil, sesame oil, tocopherol, medium-chain triglyceride, or medium-chain mono- and diglycerides. Most of the commercially available one-lipid excipient oral formulations are marketed in soft gelatin capsules and use polyethylene glycol or medium-chain triglycerides as the solubilizing excipient. Valproic acid (VPA) is one of the most widely used broad spectrum antiepileptic drug used in the treatment of both generalised and partial seizures. It is formulated as a solution in corn oil or medium chain triglycerides as 100 mg, 200 mg and 500 mg Convulex® enteric coated soft gelatin capsules. Several other VPA formulations include conventional tablets, sustained-release tablets, oral solution and intravenous solution. Even though VPA is almost completely absorbed, the absorption rate of the drug may vary according to dosage forms. Dutta and Reed evaluated five oral formulations of VPA/divalproex sodium and found that each formulation has its own advantages, limitations, distinct utility in paediatric population [123]. They evaluated VPA syrup, VPA capsule, divalproex sodium sprinkle capsule, divalproex sodium enteric-coated delayed-release tablet, and divalproex sodium extended-release tablet. These VPA/divalproex

formulations exhibited distinct pharmacokinetic and formulation characteristics. Substantial pharmacokinetic (absorption) differences were found between these five VPA/divalproex formulations, which may be rank-ordered as follows based on maximum concentration (Cmax) and time to Cmax (Tmax), VPA syrup > VPA capsule > divalproex sprinkle capsule ≅ divalproex enteric-coated delayed-release tablet > divalproex extended-release tablets. Extended-release tablets had lower mean exposure (AUC), higher apparent oral clearance (CL/F) and apparent volume of distribution (V/F), due to lower absolute bioavailability (F) compared with the other four formulations [123]. This example demonstrates the choice of formulation primarily affects the drug-release and in vivo absorption. Hence, reformulation of lipid formulation to alternative formulation requires careful investigation regarding the impact on pharmacokinetic behaviour, especially in younger children.

4.3.2. Lipid classification Type III and IV formulations (Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)

Type III and IV lipid-based formulations are those that contain mixtures of three or more excipients. Typical examples of such combinations include: (i) TPGS, polyethylene glycol (PEG) 400, and PG; (ii) oleic acid, cremophor EL, and ethanol or PG; (iii) polysorbate 20, PEG 400, and povidone; (iv) mediumchain mono- and diglycerides, -tocopherol, and povidone; (v) medium-chain triglycerides, glycol esters of fatty acids, and aspartic acid. Most of these formulations are available as soft gelatin capsules. Some marketed products of adult type III lipid formulations (see Table 2: Tipranivir, Amprenavir and cyclosporine A) are developed in oral liquid preparations for paediatric purposes, allowing flexibility in dosing down to very young ages. However, the use of these formulations that include co-solvents like ethanol, (e.g., for the cyclosporine A product Neoral®) or propylene glycol (e.g., for the Amprenavir product Agenerase®) needs to be carefully balanced against the risk and severity of the corresponding diseases that need to be treated.

Amprenavir is a protease inhibitor used in the treatment of HIV infection. It is available on the market as both an Agenerase® oral solution and soft gelatin capsule formulation, although the two preparations are not bioequivalent. The solution has a 14 % lower bioavailability than the soft gelatin capsule formulation. A single adult dose of the capsule formulation (1200 mg) contains 5.9 g PEG 400, 0.45 g propylene glycol and 3.14 g vitamin E TPGS, while the equivalent oral solution dose (1400 mg) contains15.9 g PEG 400, 51.3 g propylene glycol and 1.9 g vitamin E TPGS. This represents the estimated highest amounts of PEG 400, vitamin E TPGS and propylene glycol given orally. Due to the potential toxicity of the large dose of co-administered propylene glycol (∼1650 mg/kg per day), Amprenavir oral solution received a contraindication for infants and children below 4 years of age [124]. Intoxications due to propylene glycol have been described in children particularly in pre-term and term neonates and in infants [125]. Agenerase® has been withdrawn from marketing authorisation in US and Europe in 2010.

Ritonavir, an HIV protease inhibitor was first formulated as Norvir® soft gelatin capsules and subsequently replaced with solid dispersion tablet that exhibits desired bioavailability and acceptable ambient chemical and physical stability. Norvir® oral solution contains 80 mg/ml of ritonavir solubilised in a mixture of propylene glycol (26 % v/v), ethanol (43.2 % v/v), polyoxyl 35 castor oil, and water. The presence of ethanol and propylene glycol in the oral solution may pose risk of potential adverse effects [103]. Hence, Norvir® oral powder is developed with the intent to replace Norvir® oral solution to provide enhanced stability, favourable storage condition, absence of propylene glycol and ethanol, consistent bioavailability, and improve palatability [15]. Subsequently, SD tablet replaced the former and Norvir® oral powder is developed with the intent to replace the latter.

Microemulsion Formulations.

Microemulsions are thermodynamically stable, isotropically clear dispersions composed of a polar solvent, an oil, a surfactant, and a cosurfactant. A well-known example is the marketed SMEDDS formulation of the immunosuppressant, cyclosporine A (CsA) (Neoral®). Neoral® is a microemulsion preconcentrate containing corn oil-derived glycerides as lipids, Cremophor RH40 as a water-soluble surfactant, propylene glycol and ethanol as cosolvents, as well as DL-α-tocopherol as an antioxidant. This microemulsified cyclosporine was designed to overcome the limitation of Sandimmune®. Sandimmune®, the original lipid formulation of cyclosporine contains corn oil, Labrafil M−2125−CS and ethanol. It mixes poorly with gastrointestinal fluids, resulting in low, inconsistent absorption and does not always provide appropriate therapeutic levels. The variable absorption may expose children to the risk of rejection during episodes of gastroenteritis after liver transplantation [126]. Hence, Neoral®, a microemulsified form of cyclosporine was developed to promote stable absorption and improve bioavailability. Neoral® was shown to outperform the marketed SEDDS formulation (Sandimmune®). Several studies have compared safety and efficacy between conventional cyclosporine and microemulsified cyclosporine in children with nephrotic syndrome [127–129] and recipients of renal transplants [130,131]. These studies indicate that there may be considerable differences in CsA exposure when different formulations are administered. Neoral® formulation significantly increased the absorption (decreased Tmax), the Cmax and AUC, compared with similar doses of Sandimmune® in adults and children, which led to a dose reduction. Neoral® oral solution and Neoral® soft gelatin capsules are bioequivalent. Sandimmune® oral solution and Sandimmune® soft gelatin capsules are bioequivalent; although the inter and intra-subject variability ranges between 18 and 74 %. However, Sandimmune® and Neoral® capsules have different bioavailabilities and peak concentrations. The switch from one oral cyclosporin formulation to another should be made under physician supervision. Acott et al, identified the possible factors that result in formulation-based differences in a large group of children who received oil-based formulation cyclosporine A (CsA) over a 14-year period, before and after, and the microemulsified product were examined [132]. The study focused on whether the improvements of microemulsified product compared to CsA in the adult population also apply to children. It highlighted the need of evaluation of effect of age when introducing new formulations of drugs to paediatric patients. The main difference between these two formulations (Neoral® and Sandimmune®) is the particle size distribution (PSD) of the resulting dispersion. The droplet size in Sandimmune® and Neoral® is ranging from few nanometers to several micrometers and 100–250 nm, respectively. This difference in physicochemical characteristic resulted from a change in composition, where new surfactant like polyoxyethylated castor oil, Kolliphor ELP® with higher hydrophilic–lipophilic balance>12 was used and was shown to improve the bioavailability of cyclosporine. However, a high concentration of this surfactant in this formulation, is known to exert some adverse effects, such as hypersensitivity, nephrotoxic and anaphylactoid reactions in children [133].

4.3.3. Challenges of formulating poorly water-soluble drugs using LBDDS technology for paediatric population

The composition of a lipid-based formulation can have an influence on the in vivo performance, so an understanding of a number of parameters is important for the development of a successful lipid-based formulation. The performance of orally administered lipid-based drug formulations is crucially dependent on digestion, and understanding the colloidal structures formed during diges-

tion is necessary for rational formulation design. While lipid digestion in adults is typically a mature process, drug solubilisation in lipid, especially in young children might be significantly different due to the lower gastric volumes, lower activities of lipases, reduced bile salt secretion and differences in gastric motility patterns [11]. Some of the considerations of lipid-based formulations for paediatric patients are as below:

- Difference between infant and adult lipid digestion is the concentration and speciation of bile salts. Bile salts play a critical role in fat digestion in also in the solubilisation of lipophilic drugs. In fasting conditions, an age effect on duodenal bile salt concentrations cannot be observed and concentrations are similar in newborns and adults. However, significant differences can be observed after feeding, where concentrations in the fasted upper small intestine, and bile salt levels decrease to concentrations below the critical micelle concentration in newborns, whereas in adults a significant increase in bile salt concentration can be observed after food intake [134]. Postprandial data for other age groups are mostly lacking but the few data available indicate an increase in postprandial bile salt concentrations with increasing age.
- The need for pharmaceutically acceptable ingredients limits the choice of excipients and leads to difficulty in formulation. They require higher percentages of surfactants for formulations (usually 30–60 % of the formulation). This can cause gastrointestinal toxicity thus restricting the choice of acceptable components for paediatrics. Also, manufacturing small low-dose soft gelatin capsules can be challenging.
- Product presentation (relatively large soft gelatin capsules) presents a challenge for the use of this platform for paediatric products such as dose flexibility, administration of soft gelatin capsules. Solution presentations of these lipid vehicles, either unmodified or with the addition of cosolvents, enable the necessary dose flexibility, provided the risks associated with taste and with excipient safety can be managed.
- Another critical variable is the concentration of a drug in an oral solution, not only due to dose relative to solubility, but also taste since most drugs have poor organoleptic properties: the higher the drug concentration the poorer the taste, which can be a deterrent for children. Additionally, in an intended commercial oral solution the full adult dose should be contained within a reasonable upper volume, such as thirty milliliters, but also such that the lowest paediatric dose is contained within a measurable lower volume, such a 0.25–1.0 ml[135]. For example, Sustiva® Oral Solution, which contains 30 mg/mL of efavirenz in a vehicle of medium chain triglycerides with an antimicrobial preservative (benzoic acid) and a strawberry-mint flavour. The adult dose is 600 mg q.d (upto 20 ml) and the paediatric dose is 270–600 mg (9–20 ml). Thus the volumes of oral solution required to achieve target efavirenz AUC (>20 ml) were excessive for young subjects, particularly for those less than 3 years of age [136]. These dosing regimens deliver the maximum amount of medium-chain triglycerides per unit dose of any currently marketed oral lipid-based formulation. Another such example is the Rocaltrol® 1ug/mL oral solution formulated in a fractionated triglyceride of palm seed oil with the antioxidants, Butylated hydroxyanisole and Butylated hydroxytoluene. The paediatric dose in patients over three years of age is 0.25–0.5 μg, which is 0.25–0.5 ml daily, but for children less than three years of age the dose is 10–15 ng/kg, which is only 0.01–0.015 ml/kg daily. It is dispensed in a 15 ml multi-dose container and is supplied with 20 single-use graduated oral dispensers. Hence, the challenge is with accurate dosing of this oral solution. Many case studies have reported the issues associated with inappropriate dosing devices and medication errors [137]. To improve accuracy and safety, selection of the dosage delivery device that will work best for the patient and specific dose is required.

4.4. Nanocrystalline formulations

Among the available technologies for formulating poorly water-soluble drugs, the nanocrystal approach has achieved only limited use in commercial products. This is thought to be due to the technical complexity of physically stabilising these systems (e.g., inhibiting Ostwald ripening of nanosuspensions), the complexity and cost of transforming liquid nanocrystalline drug intermediate into a solid dosage form (e.g., by means of spray drying or spray granulation) and patent hurdles [138]. Nanocrystalline formulations are systems in which the particle size of the API is engineered to be in the range 1–100 nm or, more broadly, 1–1000 nm. Nanocrystalline systems exhibit a greater saturation solubility than a conventional particle size system per the Ostwald-Freundlich equation; however, the magnitude of this solubility boost is small for most drug formulations with particle sizes in the 10 s to 100 s of nanometres. More significant, though, is the greater dissolution rate that results from the larger surface area. Nanocrystalline formulations thus achieve higher rates and extents of oral drug absorption as compared with conventional (i.e., micron-range) particle size formulations. Various aspects of nanocrystalline formulation have been published [138–142]. There are essentially-two approaches to producing nanocrystalline APIs; these are the so-called "bottom-up" approach in which the API is crystallised to the desired particle size range and the "top-down" approach in which larger API particles are reduced in size to the desired particle size range. The top-down approach, generally using either Wet Media Milling or High-Pressure Homogenisation techniques, is most widely used for oral drug formulations for a variety of reasons. In these techniques, crystalline API is reduced in size by high intensity attrition to achieve the desired particle size. Bottom-up processes principally spray drying or solvent-antisolvent precipitation can also be used, but these can result in amorphous or partially-crystalline API and are thus more difficult to control.

These nanocrystalline APIs generally isolated as suspensions must then be further processed to yield solid materials suitable for formulating as granules, beads, tablets, capsules, film strips, or other solid forms. This "solidification" step is most often performed by means of spray drying, fluidised bed coating onto substrate particles (e.g., nonpareils), top spray fluidised bed granulation or freeze drying. Nanocrystalline materials have high surface energies by virtue of their small particle size and so stabilising excipients are needed to minimise aggregation of API particles and ensure the complete redispersibility of these particles upon dosing. Sugars, surfactants and polymers are most commonly used for this purpose. Solid dosage forms produced from solidified nanocrystalline API, when dispersed in aqueous media, frequently yield a coarser particle size distribution than the initial nanosized API. One of the primary development challenges for such products, therefore, is to identify the combination of formulation and process variables that are able to maintain the API particle size through processing, storage and subsequent dispersion in aqueous media. Liquid formulations of these nanocrystalline APIs are also theoretically feasible, although stabilising these API particles against Ostwald ripening and physical association is technically challenging. Megace® ES (megestrol acetate) Suspension is the only commercially-available example of a shelf-stable liquid formulation of nanocrystalline API for oral dosing.

Nanocrystalline formulation approaches are best suited to formulation of APIs with high crystal lattice energies. Such APIs generally have insufficient solubility in lipids to be formulated as lipid-

based systems, and may have inadequate solubility in organic solvents, too high melting points and/or inadequate miscibility with pharmaceutical polymeric to be formulated as Amorphous Solid Dispersions, whether by means of spray-drying or hot-melt extrusion.The principal advantage of the nanocrystalline approach, particularly when applied to drugs with high propensity to crystallise, is that the API is formulated as a thermodynamically-stable crystal form and thus is at low risk of physical form changes over shelf life or upon administration. In contrast, amorphous solid dispersions, lipid-based and solubilised formulations carry the risk of phase-separation and crystallisation of the drug during shelf life or upon administration, with consequent impacts on product quality and/or bioperformance. In some situations, nanocrystalline formulations have been able to mitigate the negative food effect often observed for poorly-soluble drugs, although this has not always been observed.

The principal disadvantage of the nanocrystalline formulation approach is that the nanosizing step, as outlined above, must generally be performed in a liquid medium, and the process steps needed to transform this nanocrystalline drug suspension into a solid dosage form results in a relatively complex manufacturing process with a correspondingly-high cost-of-goods. For these reasons, this approach has achieved relatively limited commercial success, although it may be well-suited for a subset of poorly-soluble drugs that are highly-crystalline or are prone to rapid crystallisation.

The first published description of this technique was by Liversidge et al in 1992 [143]. This technology was developed and commercialised by NanoSystems LLC as the NanoCrystal™ technology; NanoSystems subsequently became part of Elan Corporation. A number of nanocrystalline-based oral drug products have been successfully developed and commercialised; these commercialised products have been surveyed in several of the reviews cited, and those with paediatric indications are listed in Table 3.

The nanocrystalline approach is suitable for formulating a range of age-appropriate formulations, including capsules, tablets, orally-disintegrating tablets, minitablets, microspheres, granules and film strips. The same process technologies that are used to prepare the nanocrystalline drug suspension, solidify this suspension and convert the solidified material into adult-appropriate dosage forms can similarly be used to produce a range of age-appropriate paediatric formulations. The marketed products detailed in Table 3 illustrate that this technology can support not only conventional capsules and tablets but also a powder-in-sachet formulation for liquid dosing of infants down to 6 months of age.

4.4.1. Challenges of formulating poorly water-soluble drugs using nanocrystalline approach for paediatric population

The principal challenges of this formulation approach as it relates to paediatric drug delivery are the following.

- These nanocrystalline API particles are difficult to formulate as shelf-stable liquid (i.e., suspension) formulations due to their high surface energies. This means that liquid formulations, which provide the greatest degree of dose flexibility, can generally only be achieved through powder-for-suspension approaches that require constitution by the pharmacist or caregiver.
- Stabilising excipients are needed to minimise the aggregation of the API particles on storage and ensure the complete redispersibility of these particles upon dosing; this is especially important in situations where the API particles have been solidified and formulated as a solid dosage form. Polymers, surfactants and sugars are most commonly used for this purpose. Depending on the excipient, its level in the formulation and the paediatric age range for which the product is intended, this may present a safety concern.

This section illustrates that the nanocrystalline approach is well-suited for formulating poorly water-soluble drugs with appropriate attributes, particularly highly-crystalline drugs. In general, any drug that can be formulated using this approach for adult patients can be formulated for paediatric patients, with the limitation noted above that ready-to use (RTU) suspension formulations may not be feasible. The primary development challenge for such products, and the area most in need of further research, is to fully understand the effects of API attributes and formulation and

Table 3
Marketed paediatric products based on nanocrystalline technology.

Drug substance (Trade name, Company)	*Indication*	*Processing technology)*	*Adult formulation*	*Pediatric formulation*	*Comments*
Aprepitant (Emend®, Merck Sharp & Dohme)	Prevention of nausea & vomiting	Elan's NanoCrystal™ technology	Hard gelatin capsule formulation (adults and paediatric patients 12 years and older)	Powder in sachet for preparation of oral suspension (patients 6 months to less than 12 years).	Dose adjustment is not necessary when switching between the capsule and granule formulations. Granules for oral suspension should be prepared by healthcare provider. Once prepared, the suspension may be administered either by a healthcare provider, patient, or caregiver.
Griseofulvin (Gris-PEG®, Valeant Pharmaceuticals)	Treatment of fungal infections	Bottom-up coprecipitation technology	Scored tablet formulations, 125 mg and 250 mg strengths (adults and paediatric patients 2 years and older).	Same as adult formulations	No age-appropriate formulation *per se.* Tablets can be crushed and administered with apple sauce. Griseofulvin is dosed on a body weight basis; in increments of 62.5 mg (half a tablet). Dosage has not been established in children and infants 2 years and younger.
Sirolimus (Rapamune®, Pfizer)	Prophylaxis of organ rejection in renal transplantation	Tablet product formulated using Elan's NanoCrystal™ technology. Solution product formulated as solution in cosolvent / lipidic vehicle.	Tablet formulation (adults and paediatric patients 13 years and older).	Same as adult formulation.	The safety and efficacy of Rapamune® in paediatric patients below the age of 13 years have not been established. Oral solution contains 1.5 % – 2.5 % ethanol. Oral tablet and oral solution formulations are not bioequivalent

process variables on the stability of the API particle size through processing, storage and eventual dispersion in aqueous media.

4.5. Cyclodextrin complexation

Cyclodextrins (CDs) are a family of cyclic oligosaccharides that are produced from starch and have been largely studied and used industrially in pharmaceutical applications, due to variety of reasons such as.

- Ability to form inclusion complexes with poorly water-soluble drugs.
- Increase aqueous solubility, stability and bioavailability.
- Conversion of liquid drugs to microcrystalline powders.
- Prevention of drug-drug or drug-excipient interactions.
- Reduction of side effects such as irritation in the GI and ocular areas.
- Masking of taste and smell.

CDs are composed of at least six D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds that differ in their ring size and solubility [144] (Fig. 3). There are 3 important subtypes that naturally occur: α-CD, β-CD, and γ-CD with six, seven or eight dextrose units respectively which form a hollow truncated cone structure. This structure is composed of a hydrophilic outer surface and hydrophobic non polar internal surface. This structure gives cyclodextrins their unique characteristics of water solubility and their ability to form complexes with entrapped hydrophobic molecules.

Advantages associated with the use of cyclodextrins include the formation of inclusion complexes which result when cyclodextrins interact with appropriately sized molecules. These complexes can increase the water solubility and stability of the molecule. Adjustment of the cyclodextrin can be made which can alter the extent of drug complexation and interaction [146]. Limitations of natural CDs include low aqueous solubility relative to linear dextrins, especially βCD, and various toxicological issues, including nephrotoxicity. These liabilities have led to the development of derivatives of the native cyclodextrins with improved physicochemical properties. CD derivatives that are of particular interest to pharmaceuticals include the 2-hydroxypropyl and sulfobutylether cyclodextrins [146–148]. These derivatives serve as solubilizing excipients in medicinal products. The U.S. Food and Drug Administration (FDA) lists 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and 2-hydroxypropyl-γ- cyclodextrin (HP-γ-CD) as approved inert materials (excipients), with HPβCD being suited for oral and intravenous administration while HP-γ-CD can only be used in topical products and in a maximal concentration of 1.5 % (w/v) [149]. Sulfobutyl ether β-CD (SBE-β-CD) is non-nephrotoxic and present in several FDA-approved marketed medications for both oral and intravenous administration. HP-β-CD and SBE-β-CD have been identified as having good inclusion complexation and acceptable in vivo safety for various biomedical uses [147].

Cyclodextrins has been extensively used in a wide variety of marketed pharmaceutical products, where they are mainly used to increase the aqueous solubility, stability and bioavailability of molecules [150]. The products encompass an array of administration routes: oral, parenteral, ophthalmic, nasal and rectal [151]. However, there are few examples demonstrating the application of CDs in paediatric formulation and licensed in infants and children under 18 years of age. Examples of current licensed products include β-CD in cetirizine tablets and cisapride suppositories and cyclodextrin derivatives SBE-β-CD in the intravenous antimycotic voriconazole, HP-β-CD in the antifungal itraconazole intravenous and oral solutions, and randomly methylated (RM)-β-CD in a nasal spray for hormone replacement therapy by 17β-estradiol [145]. Selected examples of paediatric oral formulations containing cyclodextrins are discussed below.

Itraconazole (ITR) (Sporanox®) is an orally bioavailable triazole with broad-spectrum activity against a range of medically important fungi. There are a number of formulations including a capsule, cyclodextrin oral solution and an intravenous preparation. The capsules are difficult to administer to infants and children and hence are compounded extemporaneously in the dosage needed, but they need to be dissolved before administration and are difficult to administer through feeding tubes as the capsule content is gelatinous and difficult to pass through the tube. The Itraconazole oral solution hence is a significant advance over capsules. A liquid oral solution using HP-β-CD as a complex-forming agent was developed for paediatric indications and approved for use in children above 3 years old. The HP-β-CD solubilisation of itraconazole is enhanced by converting the crystalline drug to its amorphous form. The crystalline form of the drug was dissolved in acidic polyethylene glycol and then this solution was added to an

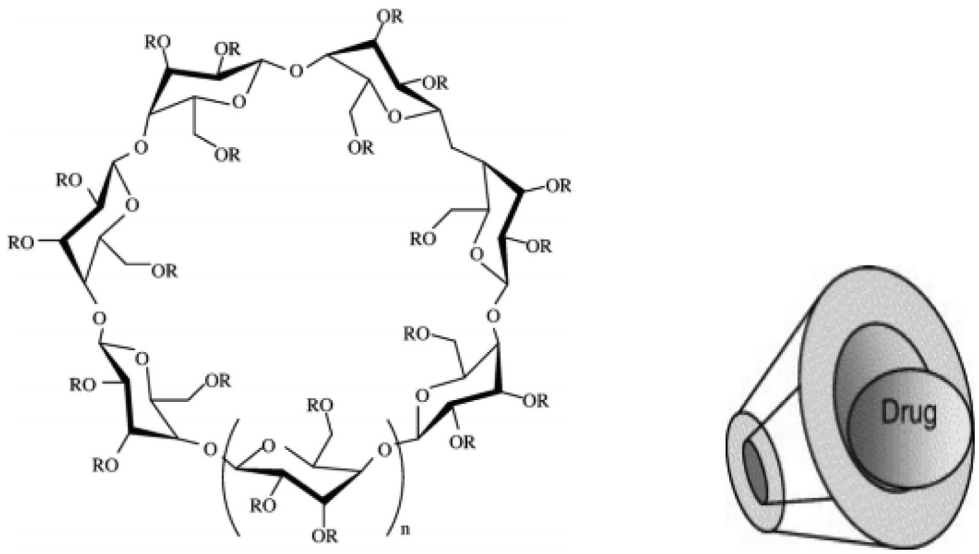

Fig. 3. Cyclodextrin structure and depiction of an inclusion complex of as drug residing in the cavity formed by the cyclodextrins (n = 0: α, n = 1: β, n = 2: γ [145].

HP-β-CD-containing aqueous solution [152]. Several studies have investigated the pharmacokinetics of the oral HP-β-CD solution of itraconazole in paediatric patients and demonstrated that up to 200 mg HP-β-CD/kg/day for 2 weeks were well tolerated and considered safe [153]. The EMA report summarises that "Above *20 mg/kg/day, cyclodextrins may show some activity, and because there are insufficient safety data in children below two years old, it is advisable to inform about the quantity of cyclodextrin in the product and that for use in children below two years old, a doctor's recommendation is needed*.".

Ozalin®, a novel oral solution of 0.2 % midazolam, is an effective option for moderate sedation prior to a therapeutic or diagnostic procedure, and as premedication before anaesthesia, in infants, children and adolescents. To overcome the problems of bitter taste and inconsistent bioavailability associated with extemporaneous formulations of oral midazolam [154,155]. Ozalin®, oral midazolam formulation was developed containing, γ-cyclodextrin, which forms inclusion complexes with midazolam, thereby enhancing the solubility and stability of midazolam solutions, and masking its bitter taste [156]. Oral administration of midazolam is preferred over invasive administration routes [157], rectal suppository [158] and intranasal spray [159], by many paediatric patients and their caregivers. A single-use filter straw and a single-use oral applicator are provided for each Ozalin® ampoule, making it easy to administer Ozalin® without the need for other supplies. As the applicator provided is graduated by bodyweight, the potential for errors in converting bodyweight-based doses to mg/mL is reduced.

In addition to the marketed formulations, continuing research is leading towards the development of paediatric formulations that incorporate the use of CDs [160]. Hydrochlorothiazide (HTZ) is one of the most commonly used diuretics in the treatment of hypertension, however commercial liquid formulations of HTZ are not available due to its limited solubility and low stability in aqueous solution, leading to complications in the administration of HTZ in paediatric patients. Regardless, HTZ is the only FDA-approved diuretic for children. To address this challenge, an innovative paediatric oral formulation of HTZ (2 mg/mL) was developed by combining the drug with HP-β-CD and SBE-β-CD and incorporation of the complex into solid lipid nanoparticles. This enabled a concomitant increased diuretic effect and a sustained drug release and, consequently, enhanced HTZ oral bioavailability after complex formation [161].

Another example includes Ramipril (Altace®), a drug commonly used for paediatric hypertension treatment. Ramipril is a highly lipophilic and poorly water-soluble drug with very low bioavailability. For adults, it is available as hard-shell capsules. There is no commercial paediatric formulation available yet. Russell et.al [162] developed an oral formulation through complex formation with HP-β-CD, that offers improved solubility when compared to the β-CD. This systematic optimisation of formulation parameters resulted in the development of oral liquid ramipril, a product that is stable for 12 months, offering preferential paediatric use over existing alternatives. However, one of the most common side effects of ramipril use is diarrhoea and cyclodextrin are capable of stimulating intestinal secretion and gastrointestinal propulsion in animals, causing diarrhoea. The increased gastrointestinal motility may be a result of the complex formation of bile salts with cyclodextrin, which leads to increased intestinal lipid concentrations. Thus, it is possible that the combination of ramipril and CDs can intensify this adverse effect, leading to increased numbers of patients suffering from these undesirable effects.

4.5.1. Challenges associated with cyclodextrins complexation technology

An inevitable limiting factor in selecting the drug for complexation is the amount of the CD complex that has to be administered [151]. The formulation bulk usually limits the amount of CD that can be included in solid dosage forms. In case of complex forming drugs, required drug dose in relation to drug molecular weight and stoichiometry of the complex determines the feasibility of oral administration of a CD inclusion complex. If a high dosage is required, large amounts of CD complex would be required. Thus, the drug/CD load may be such that it cannot be feasibly formulated into a conventional tablet of acceptable size and so other formulation possibilities such as a powder-filled sachet may need to be considered. For example, if CD (molecular weight 1135 Da) is used in a solid dosage form containing 100 mg of a drug with molecular weight 250 Da the formulation bulk will be increased by over five-fold [163].

For liquid dosage forms such as oral solutions which are the mostly used dosage form for children, it is common to use excess of CD to prevent drug precipitation upon storage and usage of the formulation. Due to formulation dilution in the gastrointestinal tract some excess CD will not hamper the drug release. However, large excess can hamper the drug release [163].

The presence of pharmaceutical excipients, such as water-soluble polymers, preservatives, and surfactants, can influence the solubilising abilities of CDs, but this depends on the excipients' physicochemical properties. Preservatives, such as propyl and methylparaben, can compete with drug molecules and expel them from the CD cavities and, thus, reduce CD solubilisation of the drugs. In addition, CD complexation of the preservatives can reduce their antimicrobial efficacy [164]. Hence, the amount of CD and the type and composition of pharmaceutical excipients used in pharmaceutical formulation needs to be carefully selected. For instance, at higher concentrations of propylene glycol (PG), the methyltestosterone solubility in presence of HP-β-CD decreased possibly due to the complex dissociation [165]. The additive or synergistic effects of excipients on the drug solubility through CD inclusion complexes have been reviewed [166].

Besides the technical challenges, there are also uncertainties around the safety of cyclodextrins in children below the age of 2 years [145]. The oral bioavailability of HP-β-CD is very low, and high doses could cause reversible diarrhoea. For children below the age of 2 years, the currently suggested permitted daily exposure of HP-β-CD is set at 16 mg/kg/day for oral ingestion [145]. The elimination of HP-β-CD strongly depends on renal clearance, and hence, a potential risk of accumulation exists in patients with renal insufficiency. In neonates and infants less than 6 months of age, renal functional maturation is still ongoing and therefore this age category might be more vulnerable for osmotic nephrosis than adults. Based on ontogeny, the lower glomerular filtration rate in young infants can lead to higher blood levels of cyclodextrins, leading to an increase in extra-renal adverse effects. The decreased renal tubular function might reduce the risk of renal toxicity due to lower intrarenal osmotic pressure. However, it is currently not known whether there is a risk of ontogeny-related direct tubular cell toxicity unrelated to osmotic pressure. Clinical data on the use of HP-β-CD in paediatrics are scarce. Hence, the use of β-CDs is limited due to low solubility in water and nephrotoxicity, especially in parenteral preparations. However, when administered orally, cyclodextrins are considered safe and devoid of toxicity, as well as poorly bioavailable since they are not extensively absorbed from the gastrointestinal system.

5. Selection of formulation approaches for poorly soluble drugs for paediatric patients

The prevalence of PWSDs in development requires access to a set of solubility-enhancing drug delivery technologies that address the challenges associated with compounds with different values of

hydrophilicity, lipophilicity, permeability and melting point. The application of these approaches for paediatric drug development can be challenging. The modification of these technologies to accommodate the needs of the paediatric population must take into account factors such as preference for liquid formulation for swallowability, taste masking, human factors (simplicity of dose preparation), and safety of excipients as shown in Fig. 4. Both technical and clinical objectives are important to consider when evaluating the most appropriate formulation strategy for paediatric formulation development.

The delivery of PWSDs for children may require the combination of the drug product with a medical device, e.g. a oral dispenser combined with further elements like cups, PiBas (press-in-bottle adapters) or enteral feeding tubes. These devices have to be carefully selected and tested with regards to their compatibility (e.g., clogging of enteral feeding tubes with solid dispersion formulations) and in-use stability (i.e. limited times for suspensions with solid dispersions). Choice of the appropriate size of an oral dispenser is key, especially if low volumes need to be administered (e.g. 0.2 ml with a 10 ml syringe is inappropriate). The compatibility of the drug product with the device needs to be analytically demonstrated.

Drug developers can leverage an integrated approach to rapidly screen formulation technologies and dosage forms in as early as the preclinical stage. Using biorelevant in-vitro screening tools and physiologically based in-silico models they can flag developability problems that could impact the downstream success of the program. User-friendly, graphical user interface (GUI) based PBPK modelling systems are now commercially available and used in paediatric drug development studies [167]. However, even though significant advances have been made, major challenges still remain in the implementation of paediatric physiology into in-silico and in-vitro setups. Many of the physiological parameters needed for accurate modeling of paediatric drug disposition are not well characterized, particularly for infants. Concerted research is needed in the development and validation of in-silico and in-vitro tools and physiology based pharmacokinetic models tailored to the paediatric population The selection of formulation strategies for PWSDs for paediatric products is summarised in Fig. 5. In general, it depends on two sets of factors (; (1) the attributes of the molecule and the disease, similar to formulation development for adults; and (2) factors related directly to the intended patient population, i.e., paediatric patients. It is the experience of the authors that adolescents ages 12–17 are generally able to swallow the adult dosage form, and that the safety and efficacy of the adult dose in this population are usually acceptable, and so the following discussion pertains primarily to the development of formulations for patients under 12 years of age. However, it is necessary to consider the particular characteristics of the disease and the patient population; for example, oncology patients may have difficulty swallowing and may require a formulation that can be administered as a liquid, possibly through a feeding tube.

Broadly speaking, the same physicochemical principles that guide the selection of formulation approaches for poorly water-

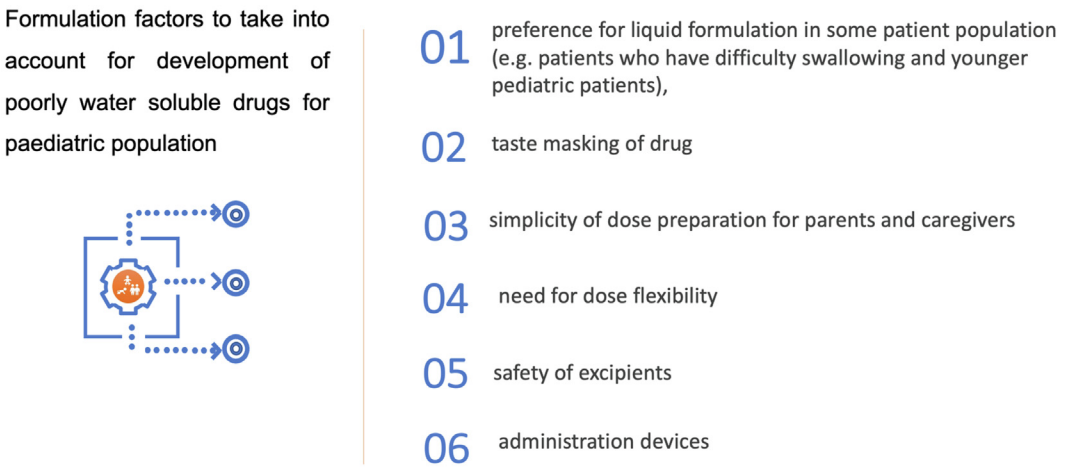

Fig. 4. Specific considerations for development of paediatric formulations.

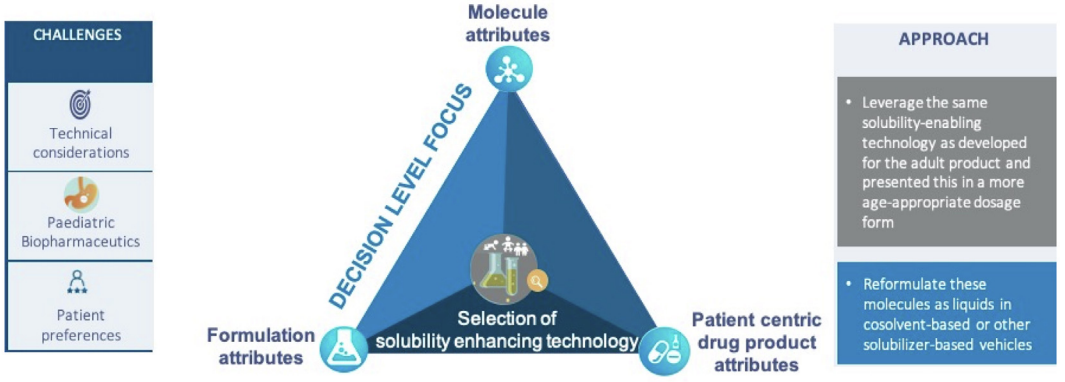

Fig. 5. Selection of solubility enhancing technology.

soluble drugs for adults also apply to the development of medicines for paediatric patients. It can be seen from the product examples in Tables 1, 2 and 3 that paediatric formulations of poorly water-soluble drugs most often use the same enabling formulation approach as the adult formulation of the same drug. This is to be expected as selection of enabling technologies is largely driven by the attributes of the molecule. For example, molecules with high octanol/water partition coefficients are generally well-suited to lipid-based formulation approaches; highly crystalline, high-melting-point drugs are likely to be well-suited to crystalline nanoparticle formulation approaches.

The second set of factors that guides the formulation development of such drugs for paediatric products relates to the particular needs of the paediatric patient population. These factors have been reviewed by many authors and recapitulated below;

- Fasted gastric fluid pH is acidic across all paediatric age groups. Only immediately after birth, in newborns, an almost neutral pH can be measured, which usually drops within the first few hours after birth. Average gastric fluid pH reported from various clinical studies across all age groups is in the range of 2–3 [64].
- Proximal intestinal (duodenal) motor activity matures throughout the first weeks of life, with increasing frequency, amplitude and duration of propagating contractions [168].
- Mechanistic paediatric oral absorption models are rather underdeveloped due to limited information surrounding age-specific differences in intestinal permeability, luminal fluid volumes and composition, and abundance of intestinal transporters. Paediatric oral absorption models are commonly parameterized in a similar manner to those of adults [169].

Small intestinal transit kinetics is well delineated among adults; however, the applicability of these values toward children remains unclear. Based on current literature, age is not found to be a significant modulator of small intestinal transit and there is no evidence to suggest that mean small intestinal transit time differs between children and adults [169].

In addition, it alsoincludes the need for dose flexibility, for the dosage form to be acceptable (e.g., swallowable) in the target patient population, for taste-masking, and for consideration of the safety of the excipients. To address these needs, formulation scientists have generally taken one of two approaches as presented in Table 4 and 5.

As can be seen from [Table 4 and Table 5] all of these paediatric formulations enable dose flexibility and can be considered age-appropriate formulations. Beyond that, it could be expected that the pellet and granule formulations would provide greater degrees of taste masking, whereas the oral solution formulations could be expected to present a greater risk of adverse taste, as well as containing higher amounts of cosolvents that are potentially undesirable in paediatric medicines. From this survey of the market, it is apparent that the majority of paediatric formulations of PWSD utilize the same solubilization technologies as the corresponding adult products, even though the presentations may be different (e.g., pellets, powder or granules rather than tablets). It can also be seen from this survey that Ritonavir (Norvir®) was initially formulated for children as a cosolvent-based solution formulation but has been subsequently reformulated as a powder-in-stick pack formulation, perhaps reflecting a trend towards powder-for-dispersion presentations and away from the use of cosolvent-based liquid formulations.

This illustrates one of the central challenges of paediatric formulation development, that optimising with respect to certain product attributes generally necessitates trade-offs with respect to other attributes; this is particularly true in the case of PWSDs, for which the formulation challenges are greater, and the degrees of freedom more limited. Particular considerations for the principal formulation approaches are summarised as follows:

- Salt formation (as discussed in Section 4.1), for ionisable compounds, is potentially-one of the simplest approaches to poor aqueous solubility as is discussed in detail in Section 4.1. Safety of the counterion, adverse taste and optimum pH are critical considerations in paediatric formulation development approaches.
- Solid dispersions (as discussed in Section 4.2) have become the most common formulation approach for new chemical entities with very low water solubility in recent years.. In paediatric

Table 4
Paediatric products which leverage the solubility-enhancing technology used in the adult formulation.

Drug substance (Trade name, Company)	Adult formulation & solubility-enabling technology	Paediatric formulation
Lopinavir/Ritonavir (Kaletra®, AbbVie for adults and Cipla ltd. for paediatric)	Tablet containing hot-melt-extruded amorphous solid dispersion	Oral pellets in capsule containing solid dispersion
Ritonavir (Norvir®, AbbVie)	Tablet containing hot-melt-extruded amorphous solid dispersion	Oral powder in stick packs containing solid dispersion
Ivacaftor (Kalydeco®, Vertex)	Tablet containing spray-dried amorphous solid dispersion	Oral granules in packet containing solid dispersion
Lumacaftor/Ivacaftor (Orkambi®, Vertex)	Tablet containing spray-dried amorphous solid dispersion	Oral granules in packet containing solid dispersion
Amprenavir (Agenerase®, GSK)	Soft gelatin capsule containing Vitamin E polyethylene glycol succinate, polyethylene glycol, propylene glycol	Oral solution containing Vitamin E polyethylene glycol succinate, polyethylene glycol, propylene glycol
Cyclosporin A (Neoral®, Novartis)	Soft gelatin capsule containing ethanol, mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, propylene glycol	Oral solution containing ethanol, mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, propylene glycol
Aprepitant (Emend®, Merck Sharp & Dohme)	Tablet containing nanocrystalline API	Powder for oral suspension containing nanocrystalline API

Table 5
Paediatric products reformulated as oral liquids.

Drug substance (Trade name, Company)	Adult formulation & solubility-enabling technology	Paediatric formulation
Ritonavir (Norvir®, AbbVie)	Tablet containing hot-melt-extruded amorphous solid dispersion	Oral solution containing ethanol, water, polyoxyl 35 castor oil, propylene glycol. Oral powder in stick packs containing solid dispersion was subsequently developed with the intent to replace oral solution; see Table 4
Lopinavir/ Ritonavir (Kaletra®, AbbVie)	Tablet containing hot-melt-extruded amorphous solid dispersion	Oral solution containing ethanol and propylene glycol
Tipranavir (Aptivus®, Boehringer Ingelheim)	Soft gelatin capsule containing lipid delivery system	Oral solution containing polyethylene glycol, vitamin E polyethylene glycol succinate, water, propylene glycol

drug formulation, the principal challenge with this mode of administration is ensuring the physical stability of the drug substance during the in-use period; i.e., assuring that the drug does not dissolve and precipitate in the product preparation prior to dosing. Importantly for paediatric dose dose flexibility can be attained by packaging these solid forms in appropriately-sized single-dose units and/or by some manipulations (dose measuring) by the parent or caregiver. Taste masking can generally be achieved by a combination of coating the solid particulates to delay drug release and a short in-use period prior to dosing.

- Lipid-based drug delivery systems are well-suited to drugs with high oil/water partition coefficients but overall are relatively infrequently used (Section 4.3). Considerations with this delivery form for paediatric patients include dose flexibility, the relatively large gelatin capsule size and excipient safety. For very young patients, differences in lipid digestion must be considered where this is necessary for the absorption of the drug.
- Nanocrystalline formulation approaches can be adapted for paediatric formulations, in very similar ways to solid dispersions (Section 4.4). Challenges include excipient safety in light of the intended patient population.. Liquid suspensions of nanocrystalline API can also be transformed into solid materials by means of spray-granulation, spray-drying, etc, which would then enable the formulation of oral granules, minitablets, etc, important in dose flexibility.
- Solution formulations based on cyclodextrins or other solubilisers and cosolvents clearly offer the greatest dose flexibility (Section 4.5). Challenges include safety of some of these excipients, or limits on their acceptable daily intakes, particularly for products intended for infants or neonates..

In the opinion of the authors, the oral delivery of poorly water-soluble drugs for paediatric patients will remain challenging for the foreseeable future. As is the case today, a significant fraction of the new molecular entities entering development will continue to be poorly-soluble molecules; none of the trends in drug discovery indicate a shift back towards lower molecular weight or more soluble structures. At the same time, the regulatory expectations (and societal pressure) to ensure age-appropriate paediatric formulations are developed where medically necessary, are likely to remain. paediatric patients are likely to remain a significant fraction of all the new drugs.

The development of solid formulations based on amorphous solid dispersions, produced by spray drying or (less commonly) by hot melt extrusion, over the past two decades has represented a major advance in oral drug delivery. While not applicable to all molecules, this technology is probably the most widely applicable of all the enabling approaches discussed in this review. It is applicable to molecules with a relatively wide range of properties, in contrast to lipid (limited to highly lipophilic) or nano (limited to highly crystalline) approaches. It is amenable to formulation of dosage forms with good patient acceptability, including tablets, minitablets, and granules for dispersion; also the excipients used in these formulations are associated with relatively few safety concerns at the levels used. Ongoing research in this field is aimed at increasing the drug loading in the SD (which would translate to smaller tablets or fewer minitablets or granules per dose) or enhancing the solubility of the drug in intestinal fluids after dissolution of the SD (which could enhance the pharmacokinetics of the drug). However, these developments are evolutionary and not revolutionary. The authors are not aware of any novel enabling technologies that are being piloted in preclinical or clinical development that are likely to enter paediatric clinical trials within the next decade or so.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] EMA, European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP),Paediatric Committee (PDCO), Guideline on pharmaceutical development of medicines for pediatric use (CHMP/QWP/180157/2011) [Online], Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf (2011).

[2] WHO, World Health Organisation, Revised WHO Classification and Treatment of Pneumonia in Children at Health Facilities: Evidence Summaries. Geneva: World Health Organization; 3, Flexible Solid Oral Dosage: Dispersible formulations of amoxicillin. Available from: https://www.ncbi.nlm.nih.gov/books/NBK264163/, (2014).

[3] N.V. Kalepu S, Insoluble drug delivery strategies: review of recent advances and business prospects., Acta Pharm Sin B., 5 (2015) 442-453.

[4] PharmaCircle: Water Insoluble Drug Development: Strategies, Technologies, Case Studies Available at https://www.pharmacircle.com/presentations/Water_Insoluble_Strategies.pdf (2011).

[5] V.J.N.-A. Stella, K. W, Prodrug strategies to overcome poor water solubility., AdV. Drug DeliVery ReV., 59 (2007) 677-694.

[6] C.A.S.W. Bergström, C. M.; Johansson, K.; Hubatsch, I. , Poorly soluble marketed drugs display solvation limited solubility., J. Med. Chem., 50 (2007) 5858 - 5862.

[7] L. Di, E.H. Kerns, Profiling drug-like properties in discovery research, Curr. Opin. Chem. Biol. 7 (2003) 402–408.

[8] K.T. Savjani, A.K. Gajjar, J.K. Savjani, Drug solubility: importance and enhancement techniques, ISRN Pharm 2012 (2012) 195727.

[9] H.K. Batchelor, J.F. Marriott, Paediatric pharmacokinetics: key considerations, Br. J. Clin. Pharmacol. 79 (2015) 395–404.

[10] J. van den Anker, M.D. Reed, K. Allegaert, G.L. Kearns, Developmental Changes in Pharmacokinetics and Pharmacodynamics, J. Clin. Pharmacol. 58 (Suppl 10) (2018) S10–S25.

[11] M.G. Mooij, B.A. de Koning, M.L. Huijsman, S.N. de Wildt, Ontogeny of oral drug absorption processes in children, Expert Opin. Drug Metab. Toxicol. 8 (2012) 1293–1303.

[12] C. Eidelman, S.M. Abdel-Rahman, Pharmacokinetic considerations when prescribing in children, Int. J. Pharmacokinet. 1 (2016) 69–80.

[13] D.P. Elder, R. Holm, M. Kuentz, Medicines for Pediatric Patients—Biopharmaceutical, Developmental, and Regulatory Considerations, J. Pharm. Sci. 106 (2017) 950–960.

[14] FDA, Sulfanilamide Disaster, FDA Consumer magazine, Available at https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf, (1981).

[15] J.B. Morris, D.A. Tisi, D.C.T. Tan, J.H. Worthington, Development and Palatability Assessment of Norvir® (Ritonavir) 100 mg Powder for Pediatric Population, Int. J. Mol. Sci. 20 (2019).

[16] W. Chin, V. Taladi, R. Savla, Considerations for formulation strategies, American Pharmaceutical Review 21 (2018).

[17] G.L. Amidon, H. Lennernäs, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 12 (1995) 413–420.

[18] J.M. Butler, J.B. Dressman, The developability classification system: application of biopharmaceutics concepts to formulation development, J. Pharm. Sci. 99 (2010) 4940–4954.

[19] W.T. Wei Lim Chin, Vijay; Savla, Ronak, Considerations for Formulation Strategies, American Pharmaceutical Review, Available at https://www.americanpharmaceuticalreview.com/Featured-Articles/354908-Considerations-for-Formulation-Strategies/, (2018).

[20] H. Merchant, F. Liu, M. Gul, A. Basit, Age-mediated changes in the gastrointestinal tract, Int. J. Pharm. 512 (2016).

[21] R. Shawahna, Pediatric Biopharmaceutical Classification System: Using Age-Appropriate Initial Gastric Volume, AAPS J. 18 (2016) 728–736.

[22] S.M. Abdel-Rahman, G.L. Amidon, A. Kaul, V. Lukacova, A.A. Vinks, G.T. Knipp, B.C.S.T.F. Members of the, Summary of the National Institute of Child Health and Human Development-best pharmaceuticals for Children Act Pediatric Formulation Initiatives Workshop-Pediatric Biopharmaceutics Classification System Working Group, Clin Ther, 34 (2012) S11-S24.

[23] S.V. Gandhi, W. Rodriguez, M. Khan, J.E. Polli, Considerations for a Pediatric Biopharmaceutics Classification System (BCS): application to five drugs, AAPS PharmSciTech 15 (2014) 601–611.

[24] H. Batchelor, Paediatric biopharmaceutics classification system: current status and future decisions, Int. J. Pharm. 469 (2014) 251–253.

[25] J.-M. delMoral-Sanchez, I. Gonzalez-Alvarez, M. Gonzalez-Alvarez, A. Navarro, M. Bermejo, Classification of WHO Essential Oral Medicines for Children Applying a Provisional Pediatric Biopharmaceutics Classification System, Pharmaceutics 11 (2019) 567.

[26] J.M. Del Moral Sanchez, I. Gonzalez-Alvarez, A. Cerda-Revert, M. Gonzalez-Alvarez, A. Navarro-Ruiz, G.L. Amidon, M. Bermejo, Biopharmaceutical

optimization in neglected diseases for paediatric patients by applying the provisional paediatric biopharmaceutical classification system, Br. J. Clin. Pharmacol. 84 (2018) 2231–2241.
[27] H. Batchelor, T. Ernest, T. Flanagan, S. Klein, R. Turner, N. Fotaki, D. Storey, Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts, Int. J. Pharm. 511 (2016) 1151–1157.
[28] Pediatric Formulations Platform, Intra-agency agreementbetween the Eunice Kennedy Shriver National Institute of ChildHealth and Human Development (NICHD) and the U.S. Food andDrug Administration (FDA) Oral Formulations Platform—Report 1. http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/upload/For-mulations_Table_for_Web_11-02-11.pdf. , (2012).
[29] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[30] T.Z. Alfredson, M., Formulation technologies to overcome poor drug-like properties, Drug Discovery Today, 9 (2012).
[31] M. Ansari, An overview of techniques for multifold enhancement in solubility of poorly soluble drugs, Current Issues in Pharmacy and Medical Sciences 32 (2019) 203–209.
[32] Y. Huang, W.-G. Dai, Fundamental aspects of solid dispersion technology for poorly soluble drugs, Acta Pharmaceutica Sinica B 4 (2014) 18–25.
[33] M. Li, M. Azad, R. Davé, E. Bilgili, Nanomilling of Drugs for Bioavailability Enhancement: A Holistic Formulation-Process Perspective, Pharmaceutics 8 (2016) 17.
[34] M. Kuentz, Lipid-based formulations for oral delivery of lipophilic drugs, Drug Discovery Today: Technologies 9 (2012) e97–e104.
[35] H. Mu, R. Holm, A. Müllertz, Lipid-based formulations for oral administration of poorly water-soluble drugs, Int. J. Pharm. 453 (2013) 215–224.
[36] T. Loftsson, M.E. Brewster, Cyclodextrins as functional excipients: methods to enhance complexation efficiency, J. Pharm. Sci. 101 (2012) 3019–3032.
[37] M. Kuentz, R. Holm, D.P. Elder, Methodology of oral formulation selection in the pharmaceutical industry, Eur. J. Pharm. Sci. 87 (2016) 136–163.
[38] D. Elder, Effective formulation development strategies for poorly soluble Active Pharmaceutical Ingredients, APIs, Pharmaceutical Outsourcing 12 (2011) 56–61.
[39] R. Harris, Formulation Strategies for 'First-Into-Man' Studies, Innovations, Pharm. Technol. (2011).
[40] P. van Hoogevest, X. Liu, A. Fahr, Drug delivery strategies for poorly water-soluble drugs: the industrial perspective, Expert Opin Drug Deliv 8 (2011) 1481–1500.
[41] T. Sam, T.B. Ernest, J. Walsh, J.L. Williams, A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms - an application for paediatric dosage form selection, Int. J. Pharm. 435 (2012) 115–123.
[42] S.R. Ranmal, A. Cram, C. Tuleu, Age-appropriate and acceptable paediatric dosage forms: Insights into end-user perceptions, preferences and practices from the Children's Acceptability of Oral Formulations (CALF) Study, Int. J. Pharm. 514 (2016) 296–307.
[43] Y. Thabet, V. Klingmann, J. Breitkreutz, Drug Formulations: Standards and Novel Strategies for Drug Administration in Pediatrics, The Journal of Clinical Pharmacology 58 (2018) S26–S35.
[44] P. Mistry, H. Batchelor, S.-U. project, Evidence of acceptability of oral paediatric medicines: a review, Journal of Pharmacy and Pharmacology, 69 (2017) 361-376.
[45] F.L. Lopez, T.B. Ernest, C. Tuleu, M.O. Gul, Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms, Expert Opinion on Drug Delivery 12 (2015) 1727–1740.
[46] M. Rautamo, K. Kvarnström, M. Sivén, M. Airaksinen, P. Lahdenne, N. Sandler, A Focus Group Study about Oral Drug Administration Practices at Hospital Wards-Aspects to Consider in Drug Development of Age-Appropriate Formulations for Children, Pharmaceutics 12 (2020) 109.
[47] I. Stoltenberg, J. Breitkreutz, Orally disintegrating mini-tablets (ODMTs) - A novel solid oral dosage form for paediatric use, European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V, 78 (2011) 462-469.
[48] A. Aleksovski, R. Dreu, M. Gašperlin, O. Planinšek, Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups, Expert Opinion on Drug Delivery 12 (2015) 65–84.
[49] S.A. Thomson, C. Tuleu, I.C.K. Wong, S. Keady, K.G. Pitt, A.G. Sutcliffe, Minitablets: New Modality to Deliver Medicines to Preschool-Aged Children, Pediatrics 123 (2009) e235–e238.
[50] M. Preis, Orally disintegrating films and mini-tablets-innovative dosage forms of choice for pediatric use, AAPS PharmSciTech 16 (2015) 234–241.
[51] R.S. Meyers, J. Thackray, K.L. Matson, C. McPherson, L. Lubsch, R.C. Hellinga, D. S. Hoff, Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List, J Pediatr Pharmacol Ther 25 (2020) 175–191.
[52] F. Kesisoglou, Y. Wu, Understanding the effect of API properties on bioavailability through absorption modeling, AAPS J. 10 (2008) 516–525.
[53] J.A. Mennella, A.C. Spector, D.R. Reed, S.E. Coldwell, The bad taste of medicines: overview of basic research on bitter taste, Clin. Ther. 35 (2013) 1225–1246.
[54] J. Martir, T. Flanagan, J. Mann, N. Fotaki, Impact of Food and Drink Administration Vehicles on Paediatric Formulation Performance: Part 1—Effects on Solubility of Poorly Soluble Drugs, AAPS PharmSciTech 21 (2020) 177.
[55] A. Siew, Formulation Strategies in Early-Stage Drug Development, Pharm. Technol. 41 (2017) 20–27.
[56] L. Zhu, L. Lu, S. Wang, J. Wu, J. Shi, T. Yan, C. Xie, Q. Li, M. Hu, Z. Liu, Chapter 11 - Oral Absorption Basics: Pathways and Physicochemical and Biological Factors Affecting Absorption, in: Y. Qiu, Y. Chen, G.G.Z. Zhang, L. Yu, R.V. Mantri (Eds.) Developing Solid Oral Dosage Forms (Second Edition), Academic Press, Boston, 2017, pp. 297-329.
[57] Y. Yang, Y. Zhao, A. Yu, D. Sun, L.X. Yu, Chapter 12 - Oral Drug Absorption: Evaluation and Prediction, in: Y. Qiu, Y. Chen, G.G.Z. Zhang, L. Yu, R.V. Mantri (Eds.) Developing Solid Oral Dosage Forms (Second Edition), Academic Press, Boston, 2017, pp. 331-354.
[58] M. Vertzoni, P. Augustijns, M. Grimm, M. Koziolek, G. Lemmens, N. Parrott, C. Pentafragka, C. Reppas, J. Rubbens, J. Van Den Abeele, T. Vanuytsel, W. Weitschies, C.G. Wilson, Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption: An UNGAP review, Eur. J. Pharm. Sci. 134 (2019) 153–175.
[59] B.J. Boyd, C.A.S. Bergström, Z. Vinarov, M. Kuentz, J. Brouwers, P. Augustijns, M. Brandl, A. Bernkop-Schnürch, N. Shrestha, V. Préat, A. Müllertz, A. Bauer-Brandl, V. Jannin, Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems, Eur. J. Pharm. Sci. 137 (2019) 104967.
[60] EMA, Reflection Paper on the Use of Extrapolation in the Development of Medicines for Paediatrics (EMA/189724/2018);, EMA: London, UK,, (2018).
[61] J.-M. Nicolas, F. Bouzom, C. Hugues, A.-L. Ungell, Oral drug absorption in pediatrics: the intestinal wall, its developmental changes and current tools for predictions, Biopharm. Drug Dispos. 38 (2017) 209–230.
[62] A.R. Maharaj, A.N. Edginton, N. Fotaki, Assessment of Age-Related Changes in Pediatric Gastrointestinal Solubility, Pharm. Res. 33 (2016) 52–71.
[63] C. Stillhart, K. Vučićević, P. Augustijns, A.W. Basit, H. Batchelor, T.R. Flanagan, I. Gesquiere, R. Greupink, D. Keszthelyi, M. Koskinen, C.M. Madla, C. Matthys, G. Miljuš, M.G. Mooij, N. Parrott, A.-L. Ungell, S.N. de Wildt, M. Orlu, S. Klein, A. Müllertz, Impact of gastrointestinal physiology on drug absorption in special populations––An UNGAP review, Eur. J. Pharm. Sci. 147 (2020) 105280.
[64] A. Neal-Kluever, J. Fisher, L. Grylack, S. Kakiuchi-Kiyota, W. Halpern, Physiology of the Neonatal Gastrointestinal System Relevant to the Disposition of Orally Administered Medications, Drug Metab. Dispos. 47 (2019) 296–313.
[65] E. Wollmer, G. Neal, M.J. Whitaker, D. Margetson, S. Klein, Biorelevant in vitro assessment of dissolution and compatibility properties of a novel paediatric hydrocortisone drug product following exposure of the drug product to child-appropriate administration fluids, Eur. J. Pharm. Biopharm. 133 (2018) 277–284.
[66] R. Banerjee, P.M. Bhatt, N.V. Ravindra, G.R. Desiraju, Saccharin Salts of Active Pharmaceutical Ingredients, Their Crystal Structures, and Increased Water Solubilities, Cryst. Growth Des. 5 (2005) 2299–2309.
[67] P.M. Bhatt, N.V. Ravindra, R. Banerjee, G.R. Desiraju, Saccharin as a salt former. Enhanced solubilities of saccharinates of active pharmaceutical ingredients, Chem Commun (Camb), (2005) 1073-1075.
[68] Z. Rahman, A. Siddiqui, M.A. Khan, Orally disintegrating tablet of novel salt of antiepileptic drug: formulation strategy and evaluation, Eur. J. Pharm. Biopharm. 85 (2013) 1300–1309.
[69] K.R. Raghavan, S.; Bembenek,K.; Benkerrour, L.; Trognon, V,; Corrao, R.; Esposito, L., Pediatric formulation of Gatifloxacin, Avialable at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2003000175&tab=PCTBIBLIOUS, 2003.
[70] S.B. Motola, A.; Agisim, G.; Quirk, D., Acid addition salt of ibuprofen and meglumine Available at https://patents.google.com/patent/US5028625A/en, Wyeth LLC, US, 1989.
[71] L.B. Bighley, SM.; Monkhouse, DC., Salt forms of drugs and absorption. Encyclopaedia of pharmaceutical Technology, (Eds: J. Swarbrick, J. C. Boylan) Vol. 13, Marcel Dekker, New York 1996, p. 453., (1996).
[72] D.P. Elder, R. Holm, H.L. Diego, Use of pharmaceutical salts and cocrystals to address the issue of poor solubility, Int. J. Pharm. 453 (2013) 88–100.
[73] M.S. Ku, Salt and polymorph selection strategy based on the biopharmaceutical classification system for early pharmaceutical development, American Pharmaceutical Review 13 (2010) 22–30.
[74] R. Bastin, M. Bowker, B. Slater, Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities, Organic Process Research & Development - ORG PROCESS RES DEV 4 (2000).
[75] A.T.M. Serajuddin and M. Pudipeddi, Salt-Selection Strategies, Handbook of Pharmaceutical Salts, P.H. Stahl and C.G. Wermuth, Eds. (Wiley-VCH, Weinheim, Germany), 2002, pp. 135–160.
[76] H. Brittain, Strategy for the prediction and selection of drug substance salt forms, 31 (2007) 78-88.
[77] G. Paulekuhn, J. Dressman, C. Saal, Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database, J. Med. Chem. 50 (2008) 6665–6672.
[78] H. Lawless, F. Rapacki, J. Horne, A. Hayes, The taste of calcium and magnesium salts and anionic modifcations, Food Qual. Prefer. 14 (2003) 319–325.
[79] S.M. Berge, L.D. Bighley, D.C. Monkhouse, Pharmaceutical salts, J. Pharm. Sci. 66 (1977) 1–19.
[80] D.G. Everett RM, Rollin M, Greener Y, Bradford JC, Benziger DP, Ward SJ. , Nephrotoxicity of pravadoline maleate (WIN 48098-6) in dogs: evidence of maleic acid-induced acute tubular necrosis Fundam Appl Toxicol, Jul;21 (1):59-65 (1993).
[81] D.P. Elder, D.J. Snodin, Drug substances presented as sulfonic acid salts: overview of utility, safety and regulation, J. Pharm. Pharmacol. 61 (2009) 269–278.

[82] E.M. Agency, Press release, 20 September 2007. CHMP Assessment report for Viracept. EMEA/H/C/164/Z/109. London, (2007).
[83] H. Stahl, Wermuth, C.G., Handbook of Pharmaceutical Salts: Properties, Selection and Use. Wiley-VCH Weinheim, (2002).
[84] P.H. Stahl, Wermuth, C.G. , Monographs on acids and bases. Handbook of Pharmaceutical Salts: Properties, Selection and Use, pp. 265-327. P.H. Stahl C. G. Wermuth Wiley-VCH Weinheim, (2002).
[85] E.A. Thackaberry, Non-clinical toxicological considerations for pharmaceutical salt selection, Expert Opin. Drug Metab. Toxicol. 8 (2012) 1419–1433.
[86] S.G. Olovson, N. Havu, C.G. Regårdh, A. Sandberg, Oesophageal ulcerations and plasma levels of different alprenolol salts: potential implications for the clinic, Acta Pharmacol Toxicol (Copenh) 58 (1986) 55–60.
[87] EMA, Committee for Medicinal Products for Human Use (CHMP), Assessment report: Nitrosamine impurities in human medicinal products. Available at https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf, (2020).
[88] ATSDR, Agency for Toxic Substances and Disease Registry. Toxicological profile for Nitrate and Nitrite. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service., (2017).
[89] C. Agatemor, K.N. Ibsen, E.E.L. Tanner, S. Mitragotri, Ionic liquids for addressing unmet needs in healthcare, Bioeng. Transl. Med. 3 (2018) 7–25.
[90] A.T. Serajuddin, Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs, J. Pharm. Sci. 88 (1999) 1058–1066.
[91] F. Meng, V. Dave, H. Chauhan, Qualitative and quantitative methods to determine miscibility in amorphous drug-polymer systems, Eur. J. Pharm. Sci. 77 (2015) 106–111.
[92] G. Paudwal, N. Rawat, R. Gupta, A. Baldi, G. Singh, P.N. Gupta, Recent Advances in Solid Dispersion Technology for Efficient Delivery of Poorly Water-Soluble Drugs, Curr. Pharm. Des. 25 (2019) 1524–1535.
[93] J. Breitenbach, Melt extrusion: from process to drug delivery technology, Eur. J. Pharm. Biopharm. 54 (2002) 107–117.
[94] D.C.T. Tan, J.J. Ong, R. Gokhale, P.W.S. Heng, Hot melt extrusion of ion-exchange resin for taste masking, Int. J. Pharm. 547 (2018) 385–394.
[95] EMA/CHMP/ICH/82260/2006, ICH guideline Q3C (R5) on impurities: guideline for residual solvents, (2015).
[96] D.C. Tan, W.W. Chin, E.H. Tan, S. Hong, W. Gu, R. Gokhale, Effect of binders on the release rates of direct molded verapamil tablets using twin-screw extruder in melt granulation, Int. J. Pharm. 463 (2014) 89–97.
[97] R. Jog, S. Kumar, J. Shen, N. Jugade, D.C. Tan, R. Gokhale, D.J. Burgess, Formulation design and evaluation of amorphous ABT-102 nanoparticles, Int. J. Pharm. 498 (2016) 153–169.
[98] P. Tran, Y.C. Pyo, D.H. Kim, S.E. Lee, J.K. Kim, J.S. Park, Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs, Pharmaceutics 11 (2019).
[99] R. Ternik, F. Liu, J.A. Bartlett, Y.M. Khong, D.C. Thiam Tan, T. Dixit, S. Wang, E. A. Galella, Z. Gao, S. Klein, Assessment of swallowability and palatability of oral dosage forms in children: Report from an M-CERSI pediatric formulation workshop, Int. J. Pharm. 536 (2018) 570–581.
[100] B. Farkas, A. Balogh, A. Farkas, A. Domokos, E. Borbás, G. Marosi, Z.K. Nagy, Medicated Straws Based on Electrospun Solid Dispersions, Periodica Polytechnica, Chem. Eng. 62 (2018) 310–316.
[101] J. Chen, J.D. Ormes, J.D. Higgins, L.S. Taylor, Impact of surfactants on the crystallization of aqueous suspensions of celecoxib amorphous solid dispersion spray dried particles, Mol. Pharm. 12 (2015) 533–541.
[102] Prescribing Information. Kaletra (lopinavir and ritonavir) https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf. Accessed on 11 Dec 2020.
[103] Prescribing Information. Norvir (ritonavir) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209512lbl.pdf Accessed on 11 Dec 2020.
[104] Prescribing Information. Lopinavir and Ritonavir Oral Pellets 40 mg/10 mg. https://www.accessdata.fda.gov/drugsatfda_docs/pepfar/205425PI.pdf. Accessed on 11 Dec 2020.
[105] Prescribing Information. Intelence (etravirine). Accessed on 11 Dec 2020.
[106] R. Bortolussi, S. Martin, C.P. Society, I. Diseases, I. Committee, Antifungal agents for common outpatient paediatric infections, Paediatrics & Child Health, 12 (2007) 875-878.
[107] Prescribing Information. Sporanox (Itraconazole) https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020083s040s041s044lbl.pdf. Accessed on 11 Dec 2020.
[108] Drugs.com, Onmel (Itraconzole) https://www.drugs.com/pro/onmel.html. Accessed on 13 Dec 2020.
[109] EMA, Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006: Noxafil posaconazole, Available at https://www.ema.europa.eu/en/documents/variation-report/noxafil-h-c-610-p46-0029-epar-assessment-report_en.pdf, (2019).
[110] Prescribing Information. Prograf (Tacrolimus) https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf. Accessed on 11 Dec 2020.
[111] EMA, **Assessment report for Modigraf (Tacrolimus)**, Available at https://www.ema.europa.eu/en/documents/assessment-report/modigraf-epar-public-assessment-report_en.pdf, (2009).
[112] Kalydeco website https://www.kalydeco.com/ Accessed on 11 Dec 2020.
[113] Prescribing Information. Kalydeco (Ivacaftor) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203188s022l_207925s003lbl.pdf. Accessed on 11 Dec 2020.
[114] N.L. Trevaskis, W.N. Charman, C.J. Porter, Lipid-based delivery systems and intestinal lymphatic drug transport: a mechanistic update, Adv. Drug Deliv. Rev. 60 (2008) 702–716.
[115] R. Savla, J. Browne, V. Plassat, K.M. Wasan, E.K. Wasan, Review and analysis of FDA approved drugs using lipid-based formulations, Drug Dev. Ind. Pharm. 43 (2017) 1743–1758.
[116] H. Shrestha, R. Bala, S. Arora, Lipid-Based Drug Delivery Systems, Journal of Pharmaceutics 2014 (2014) 801820.
[117] R.G. Strickley, Solubilizing Excipients in Oral and Injectable Formulations, Pharm. Res. 21 (2004) 201–230.
[118] X. Chen, O. Gudmundsson, M. Hageman, Application of lipid-based formulations in drug discovery, J. Med. Chem. 55 (2012) 7945–7956.
[119] D.H. Benameur, Lipid-based Dosage Forms-An emerging platform for drug delivery.
[120] C.W. Pouton, Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems, Eur. J. Pharm. Sci. 11 (2000) S93–S98.
[121] C.W. Pouton, Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system, Eur. J. Pharm. Sci. 29 (2006) 278–287.
[122] H.D. Williams, P. Sassene, K. Kleberg, M. Calderone, A. Igonin, E. Jule, J. Vertommen, R. Blundell, H. Benameur, A. Müllertz, C.J. Porter, C.W. Pouton, Toward the establishment of standardized in vitro tests for lipid-based formulations, part 4: proposing a new lipid formulation performance classification system, J. Pharm. Sci. 103 (2014) 2441–2455.
[123] S. Dutta, R.C. Reed, Distinct absorption characteristics of oral formulations of valproic acid/divalproex available in the United States, Epilepsy Res. 73 (2007) 275–283.
[124] EMA, Agnerase: Summary of Product Characteristics Available at https://ec.europa.eu/health/documents/community-register/2005/2005082410158/anx_10158_en.pdf, (2005).
[125] EMA, Committee for Human Medicinal Products (CHMP), Background review for the excipient propylene glycol, Available at https://www.ema.europa.eu/en/documents/report/background-review-excipient-propylene-glycol-context-revision-guideline-excipients-label-package_en.pdf, EMA/CHMP/334655/2013 (2014).
[126] D. Colombo, C.G. Egan, Bioavailability of Sandimmun® versus Sandimmun Neoral®: a meta-analysis of published studies, Int.. J. Immunopathol. Pharmacol. 23 (2010) 1177–1183.
[127] A.K. Trull, K.K. Tan, L. Tan, G.J. Alexander, N.V. Jamieson, Enhanced absorption of new oral cyclosporin microemulsion formulation, Neoral, in liver transplant recipients with external biliary diversion, Transplant Proc 26 (1994) 2977–2978.
[128] P. Niaudet, O. Reigneau, H. Humbert, A pharmacokinetic study of Neoral in childhood steroid-dependent nephrotic syndrome, Pediatr. Nephrol. 16 (2001) 154–155.
[129] S. Pollard, B. Nashan, A. Johnston, P. Hoyer, P. Belitsky, P. Keown, H. Helderman, A pharmacokinetic and clinical review of the potential clinical impact of using different formulations of cyclosporin A, Clin. Ther. 25 (2003) 1654–1669.
[130] I.D. van Mourik, M. Thomson, D.A. Kelly, Comparison of pharmacokinetics of Neoral and Sandimmune in stable pediatric liver transplant recipients, Liver Transpl Surg 5 (1999) 107–111.
[131] S.G. Pollard, P.A. Lear, A.R. Ready, R.H. Moore, R.W. Johnson, Comparison of microemulsion and conventional formulations of cyclosporine A in preventing acute rejection in de novo kidney transplant patients. The U.K. Neoral Renal Study Group, Transplantation 68 (1999) 1325–1331.
[132] P.D. Acott, J.F. Crocker, K.W. Renton, Evaluation of performance factors affecting two formulations of cyclosporine in pediatric renal transplant patients, Transplant Proc 38 (2006) 2835–2841.
[133] H. Gelderblom, J. Verweij, K. Nooter, A. Sparreboom, Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation, Eur. J. Cancer 37 (2001) 1590–1598.
[134] L. Poquet, T.J. Wooster, Infant digestion physiology and the relevance of in vitro biochemical models to test infant formula lipid digestion, Mol. Nutr. Food Res. 60 (2016) 1876–1895.
[135] P. Augustijns, M. Brewster, Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics, Springer-Verlag New York, VI (2007).
[136] EMA, Committee for Medicinal Products for Human Use (CHMP), Assessment report Sustiva; Available at: https://www.ema.europa.eu/en/documents/scientific-discussion-variation/sustiva-h-c-249-ii-0126-g-epar-scientific-discussion-variation_en.pdf, EMA/260283/2015, (2015).
[137] Institute for Safe Medication Practices, Preventing medication errors involving different formulations of cyclosporine, PharmacyToday, 25 (2019) 36.
[138] H.D. Williams, N.L. Trevaskis, S.A. Charman, R.M. Shanker, W.N. Charman, C. W. Pouton, C.J. Porter, Strategies to address low drug solubility in discovery and development, Pharmacol. Rev. 65 (2013) 315–499.
[139] M. Malamatari, K.M.G. Taylor, S. Malamataris, D. Douroumis, K. Kachrimanis, Pharmaceutical nanocrystals: production by wet milling and applications, Drug Discov Today 23 (2018) 534–547.
[140] A. Chen, Y. Shi, Z. Yan, H. Hao, Y. Zhang, J. Zhong, H. H., Dosage form developments of nanosuspension drug delivery system for oral

administration route, Current pharmaceutical design 21 29 (2015) 4355-4365.
[141] M.L. Chen, M. John, S.L. Lee, K.M. Tyner, Development Considerations for Nanocrystal Drug Products, AAPS J. 19 (2017) 642–651.
[142] S.V. Jermain, C. Brough, R.O. Williams 3rd, Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery - An update, Int. J. Pharm. 535 (2018) 379–392.
[143] G.G. Liversidge, Cundy, K.C., Bishop, J.F. & Czekai, D.A., Surface modified drug nanoparticles, US Patent 5,145,684., (1992).
[144] Z. Li, M. Wang, F. Wang, Z. Gu, G. Du, J. Wu, J. Chen, γ-Cyclodextrin: a review on enzymatic production and applications, Appl. Microbiol. Biotechnol. 77 (2007) 245–255.
[145] EMA, Committee for Human Medicinal Products (CHMP) Cyclodextrins used as excipients Report published in support of the 'Questions and answers on cyclodextrins used as excipients in medicinal products for human use, EMA/CHMP/495747/2013, (2013).
[146] T. Loftsson, M.E. Brewster, Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization, J. Pharm. Sci. 85 (1996) 1017–1025.
[147] V.J. Stella, Q. He, Cyclodextrins, Toxicol. Pathol. 36 (2008) 30–42.
[148] L. Szente, J. Szejtli, Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development, Adv. Drug Deliv. Rev. 36 (1999) 17–28.
[149] S.S. Braga, Cyclodextrins: Emerging Medicines of the New Millennium, Biomolecules 9 (2019) 801.
[150] T. Loftsson, P. Jarho, M. Másson, T. Järvinen, Cyclodextrins in drug delivery, Expert Opinion on Drug Delivery 2 (2005) 335–351.
[151] J. Szejtli, Cyclodextrin Complexed Generic Drugs are Generally not Bio-equivalent with the Reference Products: Therefore the Increase in Number of Marketed Drug/Cyclodextrin Formulations is so Slow, J. Incl. Phenom. Macrocycl. Chem. 52 (2005) 1–11.
[152] T. Loftsson, M.E. Brewster, Pharmaceutical applications of cyclodextrins: basic science and product development, J. Pharm. Pharmacol. 62 (2010) 1607–1621.
[153] A.K. Gupta, E.A. Cooper, G. Ginter, Efficacy and safety of itraconazole use in children, Dermatol. Clin. 21 (2003) 521–535.
[154] B. Isik, O. Baygin, H. Bodur, Effect of drinks that are added as flavoring in oral midazolam premedication on sedation success, Paediatr Anaesth. 18 (2008) 494–500.
[155] S.L. Steedman, J.R. Koonce, J.E. Wynn, N.H. Brahen, Stability of midazolam hydrochloride in a flavored, dye-free oral solution, Am J Hosp Pharm 49 (1992) 615–618.
[156] K.A. Lyseng-Williamson, Midazolam oral solution (Ozalin®): a profile of its use for procedural sedation or premedication before anaesthesia in children, Drugs & Therapy, Perspectives 35 (2019) 255–262.
[157] M. Rafeey, M. Ghojazadeh, Oral midazolam in pediatric upper gastrointestinal endoscopy, J. Gastroenterol. Hepatol. 5 (2012) 104.
[158] Y.S. Aydintug, K.M. Okcu, Y. Guner, Y. Gunaydin, M. Sencimen, Evaluation of oral or rectal midazolam as conscious sedation for pediatric patients in oral surgery, Mil. Med. 169 (2004) 270–273.
[159] M. Manoj, M.V.S. Satya Prakash, S. Swaminathan, R.K. Kamaladevi, Comparison of ease of administration of intranasal midazolam spray and oral midazolam syrup by parents as premedication to children undergoing elective surgery, J Anesth 31 (2017) 351–357.
[160] Q. Alves, S. Camargo, R. Cruz de Jesus, D. Silva, Drugs–β-Cyclodextrin inclusion complex: Would be a new strategy to improve Antihypertensive Therapy? Clin Res Trials, Available at https://www.oatext.com/drugs-cyclodextrin-inclusion-complex-would-be-a-new-strategy-to-improve-antihypertensive-therapy.php#Article_Info, (2019).
[161] M. Cirri, N. Mennini, F. Maestrelli, P. Mura, C. Ghelardini, L. Di Cesare Mannelli, Development and in vivo evaluation of an innovative "Hydrochlorothiazide-in Cyclodextrins-in Solid Lipid Nanoparticles" formulation with sustained release and enhanced oral bioavailability for potential hypertension treatment in pediatrics, Int. J. Pharm. 521 (2017) 73–83.
[162] C. Russell, S. Begum, Y. Hussain, M. Hussain, D. Huen, A.S. Rahman, Y. Perrie, A.R. Mohammed, Paediatric drug development of ramipril: reformulation, in vitro and in vivo evaluation, J. Drug Target. 23 (2015) 854–863.
[163] P. Saokham, C. Muankaew, P. Jansook, T. Loftsson, Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes, Molecules 23 (2018).
[164] I.R. Embrechts, M. François, J. Peeters, I. Van Assche, The Influence of Hydroxypropyl-B-Cyclodextrin In The Activity Of Antimicrobial Preservatives For Oral Pharmaceutical Products, Proceedings of International Cyclodextrin Symposium, (2004) 799-804.
[165] B.W. Müller, E. Albers, Effect of hydrotropic substances on the complexation of sparingly soluble drugs with cyclodextrin derivatives and the influence of cyclodextrin complexation on the pharmacokinetics of the drugs, J. Pharm. Sci. 80 (1991) 599–604.
[166] T. Loftsson, Increasing the cyclodextrin complexation of drugs and drug biovailability through addition of water-soluble polymers, Pharmazie 53 (1998) 733–740.
[167] M. Van der Veken, J. Brouwers, V. Budts, L. Lauwerys, S.M. Pathak, H. Batchelor, P. Augustijns, Practical and operational considerations related to paediatric oral drug formulation: An industry survey, Int. J. Pharm. 618 (2022) 121670.
[168] D. Bar-Shalom, K. Rose, Pediatric Formulations: A Roadmap, Springer New York2014.
[169] A.R. Maharaj, A.N. Edginton, Examining Small Intestinal Transit Time as a Function of Age: Is There Evidence to Support Age-Dependent Differences among Children?, Drug Metab Dispos. 44 (2016) 1080–1089.
[170] Prescribing Information. Afinitor (Everolimus) https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022334s6lbl.pdf Accessed on 11 Dec 2020.