# From Supersaturated Drug Delivery Systems to the Rising Era of Pediatric Formulations

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The number of options available to drug discovery scientists to enhance the solubility of poorly soluble compounds by conventional formulation approaches is limited. In most cases, drug formulation is oriented toward the creation of a supersaturated solution upon contact with aqueous environment, often combined with solubilizing agents and precipitation inhibitors. The most popular formulations for achieving this target are the lipid-based formulations called self-emulsifying and self-microemulsifying drug delivery systems, SEDDS and SMEDDS, respectively. They offer enhanced absorption and hence enhanced oral bioavailability of lipophilic drugs, presenting the drug in solubilized form *in vivo,* avoiding dissolution, which can be the rate limiting step in drug absorption for sparingly soluble drugs. The production of high energy or rapid dissolving solid state formulations using drug particle engineering to enhance drug solubility and bioavailability is also applied. These formulations include solid dispersions, nanoparticles, co-ground mixtures etc. Furthermore, the development of prodrugs is also a useful strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the developability and usefulness of a potential drug. Up to now, most medications were made for adults and children's requirements were not taken into account. Since the recent adoption of Paediatric Regulations in the U.S. and E.U., there is a greater demand for age-appropriate medicines for children. The challenges in paediatric formulation development are mostly associated with the difficulty in defining design requirements for the intended dosage form that is most appropriate for the target patient population, due to the diversity of the paediatric population (range of ages, physical size and capabilities) that varies significantly from birth to age 12 yrs old along with the dosage flexibility. The last years there has been an effort to develop solid paediatric formulations that deliver the appropriate dose in a "user friendly" way and to find alternative drug delivery vehicles, such as mini-tablets, dairy products, and new taste masking techniques in order to improve drug acceptability. In addition, alternative routes of administration have been proposed such as inhalation and nasal administration.

*Key words:*
Supersaturation, solubility, dissolution, drug delivery systems, pediatric formulations

## Introduction

The majority of pharmacologically active new chemical entities exhibit extremely poor aqueous solubility (less than 10 μM or 5 μg/mL for a compound with a molecular weight of 500)[1] and good permeability, and these characteristics result to low bioavailability. The number of options available to drug discovery scientists to enhance the solubility of a compound by conventional formulation approaches, is limited. In case of ionizable compounds the identification and selection of stable pharmaceutical salts is the most popular technique[2]. Other common strategies include the reduction of solid particle size by micronization, such as milling[3], or the formation of nanosuspensions,[4] the use of complexation agents such as cyclodextrins,[5] or the use of solubilizing excipients.[6] In most cases, the formulation of poorly water soluble compounds is oriented toward the creation of a supersaturated solution upon contact with aqueous environment, often combined with solubilizing agents and precipitation inhibitors.[3] The main target of such formulation is to present the drug in supersaturated concentration for an extended period of time, achieving maintenance of the drug's concentration in high levels.

The most popular formulations for achieving this target, are the lipid-based formulations, such as self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS, respectively) oil solutions. They offer enhanced absorp-

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tion and hence enhanced oral bioavailability of lipophilic drugs[7]. These formulations present the drug in solubilized form *in vivo,* avoiding dissolution, which can be the rate limiting step in drug absorption for sparingly soluble drugs.[8,9] As the absorption of poorly water-soluble drugs is substantially enhanced by coadministration with food rich in triglycerides there have been developed lipid systems mimicking the solubilization provided by foodstuffs.[10,11] Moreover, the latest trend is the effort to develop paediatric formulations that deliver the appropriate dose in a "user friendly" way, finding alternative drug delivery vehicles that enhance solubility and bioavailability, such as dairy products.[12] The main characteristic of a successful lipid formulation is the ability to maintain the drug in solution in the stomach and throughout the intestine. This is extremely challenging, as the majority of poorly soluble drugs are more soluble in formulations as they are diluted, while they precipitate after dispersion of the drug in the intestine.

This large group of formulations, called lipid formulations, have common characteristics, but they can be differentiated by the extent to which they disperse in water and their digestibility, ranging from a simple oily formulation dispersed by digestion in the small intestine through to more complex self-emulsifying and microemulsion systems. Lipid systems generally include triglycerides, mono and diglycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents; excipients with a wide variety of physicochemical properties. The lipid formulation classification system (LFCS) was first proposed by Pouton in 2000[13], providing a framework for comparing formulations which in practice could include a wide variety of different excipients. The formulations are categorized in four types. Type I includes formulations which are oils (triglycerides or mixed mono and diglycerides) and require digestion to facilitate dispersion. Type II formulations, are self-emulsifying, have no water soluble components and produce relatively coarse emulsions in the 0.25–2 mm range. These are mostly oils and water insoluble ester ethoxylates (nonionic surfactants with HLB values of approximately 11). Type III formulations include water-soluble components and produce very fine dispersions (<100 nm, optically clear). They can be subdivided into Type IIIA and IIIB, based on the proportion of water-soluble surfactants and cosolvents that include. Type IV formulations were included in lipid formulation classification system (LFCS)[14] in 2006. They do not contain any lipid and produce fine micellar solutions depending on the surfactant concentration.

There are many studies that point out the significance of the dispersion phase for poorly water-soluble drugs. Depending on the composition of the lipid-based formulation, the drug is maintained in solution in the lumen of the gastrointestinal tract prior to absorption, after dispersion and during digestion of the formulation.[15] For example, the study published by Mohsin et al. in 2009 about fenofibrate[15] (Class II drug), demonstrated that Type II and Type IIIA formulations often maintained the drug in a supersaturated state for several hours after dispersion, but Type IIIB and Type IV formulations, which contained a higher proportion of water-miscible excipients, typically lost solvent capacity quickly on dispersion.

## Supersaturated *in vitro* solubility and dissolution data

Recent studies dealing with kinetic solubility and supersaturated phenomena[16,17] place particular emphasis on the relevance of supersaturated solubility with the absorption of orally administered drugs and their biopharmaceutic classification. Moreover, supersaturated solubilities are frequently found in studies measuring drug concentrations in human aspirates[18,19] while the subsequent precipitation of drug has been the subject of several studies.[20,21] Recently, a study[22] of the effect of supersaturation on oral drug absorption revealed that formulation technology that can induce supersaturation may be of great assistance to the successful development of poorly water-soluble drugs. In the same vein, stable supersaturated milk based formulations of NSAIDs were prepared with satisfactory in vivo performance.[12]

Studies dealing with supersaturated dissolution data for poorly water-soluble drugs are roughly divided into two categories. In the first set of the studies, the preparation of a high energy meta-stable form in an amorphous or semi-crystalline state is described.[23,24] Usually, the solubility of the amorphous polymorphs is much higher than that of its crystalline form.[24] This results in an increased dissolution rate and an enhancement of bioavailabity.[25] However, it is not uncommon to observe a progressive diminution of drug concentration during the dissolution process due to the kinetic instability of the high energy amorphous drug.[26,27] This type of studies of the enhanced solubility-dissolution rate is routinely explained via the increased saturation solubility, $C_s$, in accord with the well known Noyes-Whitney equation (Eq.1):

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{DA}{h}(C_s - C) \tag{1}$$

where $D$ is the diffusivity, $A$ is the specific area of the particles, $h$ is the diffusion layer path length in the boundary layer about the particle, $C_s$ is the solu-

bility of the drug, and $C$ is the concentration of drug in solution at time $t$.

In the second set of studies, the dissolution of poorly soluble drugs is studied in the presence of various additives e.g. surfactant agents, polymers, food constituents.[28–30] An initial very high dissolution rate is usually observed which leads to concentration values higher than the solubility level. When these higher than saturation solubility values are maintained and are justified by independent solubility experiments in the presence of additives, the high rate of dissolution can be explained on the basis of Eq.1. However, in several studies the supersaturated levels subsequently relax towards the saturation solubility.[31] This type of non-monotonic dissolution curves cannot be explained using the classical diffusion layer model. Instead, the reaction limited model of dissolution seems to be more appropriate to interpret these data. The model relies on the bidirectional chemical reaction of the solid species $s$ with $n$ free solvent molecules $w$, yielding the dissolved species of drug complex with solvent $c$:

$$s + nw \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} c \tag{2}$$

where $k_1$ and $k_{-1}$ are the forward and backward microconstants. The major characteristic of this model is that the rate of dissolution is not governed by the saturation solubility. In this model, the saturation solubility of the drug, $C_s$ in the dissolution medium is the result of the chemical equilibrium of reaction 2 and corresponds to the concentration at steady state, $C_{ss}$ when the drug dose, $M_0$ used is in excess[29]:

$$C_{ss} = \frac{k_1^*}{k_1^* + k_{-1}} \frac{M_0}{V} \tag{3}$$

where $V$ is the volume of the dissolution medium and $k_1^*$ is a composite rate constant related to $k_1$.

The rate of the dissolution process is given by the velocity of the unidirectional reaction 2 and is (as derived in 29):

$$\frac{dC}{dt} = k_1^* \left( \frac{M_0}{V} - C \right)^a - k_{-1} C \tag{4}$$

where $C$ is the concentration of the dissolved drug, $k_1^* = k_1[w_0]^b$, $M_0$ is the initial quantity (dose) in mass units, $\alpha$ and $b$ are constants related to stoichiometry of the reaction and also to the geometry of the particles.

Although in the original work[29] $k_1^*$ was assumed to be constant, a time dependant expression of the following form may also be appropriate:

$$k_1^* = K \cdot t^{-h} \tag{5}$$

Expressions of this form have been used before to account for time variable rate coefficients, due to understirring and crowding in the microenviroment of the reaction.[30,31] This approach is often referred to as fractal kinetics and has implications and physical meaning beyond an empirical time dependant coefficient. In order to avoid infinity at time zero a similar to Eq. 5 expression is considered:

$$k_1^* = K(g + (1 + t)^{-h}) \tag{6}$$

where $K$ is a constant while $g$ is a constant prohibiting the entire expression to approach zero for large times.

Equations 4 and 6 describe a dissolution process in which the equilibrium and therefore solubility as given by equation 3 is initially higher and drops with time.[32]

## "Supersaturated" drug delivery systems

The most commonly used approach to enhance oral bioavailability of poorly soluble drugs, is to administer the drug in solution in order to escape the dissolution process step. To this end various solubilizing agents are used such as oils, surfactants, hydrophilic co-solvents and complexing molecules e.g. cyclodextrins to solubilize the poorly water soluble drug[3,33–36]. An important approach is the self-emulsifying or self-micro-emulsifying drug delivery systems (SEDDS, SMEDDS), consisting of a combination of oils with co-solvent and/or surfactants to form oil-in-water emulsions or micro-emulsions where the drug is completely dissolved.[3,37–40] The most notable example of commercially available "micro-emulsion formulation" is the cyclosporine formulation Neoral®. The concentration of drug in the microemusion (5000mg/50mL) is 100 mg/mL (www.pharma.us.novartis.com/product/pi/pdf/neoral.pdf) which is more than 10000 times higher than its aqueous solubility ($7.3 \times 10^{-3}$ mg/mL, 37°C).[36] Self-microemulsifying drug delivery systems of Class II drugs like itraconazole,[37] paclitaxel[38] and fenofibrate[39] have been also reported in literature. However, by entering the gastrointestinal (GI) tract drug may precipitate from SEDDS. The capacity of GI fluids to keep the drug in solution is an indicator of the success of the SEDDS. In addition, in the case of very lipophilic drugs, despite successful solubilization, the free drug concentration may be very low to result in significant intestinal absorption and systemic exposure. A more recent approach is the supersaturated SEDDS (S-SEDDS) which attempt to generate high supersaturated free drug concentrations in the gastrointestinal tract and to reduce drug precipitation rate allowing for

sufficient absorption.[3,40] S-SEDDS contain reduced amount of surfactant and a precipitation inhibitor such as hydroxyl-propyl-methylcellulose (HPMC). The first drug formulated as S-SEDDS is paclitaxel with an aqueous solubility <1 $\mu$g/mL. The S-SEDDS of paclitaxel contains less surfactant (cremophor® EL) than the solubilized formulation Taxol® and the precipitation rate of the drug is reduced by the incorporation of 5% HPMC in the formulation.[40]

In addition to SEDDS, a number of solid state formulation drug delivering systems have been developed, that can induce supersaturated drug concentrations in the GI tract. These systems incorporate drug in a high energy (HE) or rapidly dissolving form (RDF).[41] The production of HE or RDF of a drug requires drug particle engineering such as milling, cogriding, melting, freeze-drying etc. in order to alter the size, morphology and/or wettability of drug particles.[42] Reduction of particle size, in conjunction to improved wettability, usually results in enhanced dissolution rate by increasing the available for dissolution drug surface area which also leads to increased apparent drug solubility (i.e. the equilibrium between drug in solution and a solid form of the drug that is not in the most stable state.[42,43]

Supersaturated solid drug formulations include solid dispersions, nanoparticles, co-ground mixtures, crystalline salt forms of the drug, water soluble prodrugs and the use of inorganic carrier based delivery systems.

Solid dispersions contain the drug in the amorphous state dispersed in a hydrophilic polymeric matrix such as polyvinylpyrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), polyethyleneglycole (PEG), or combination of polymers, as well as surfactants such as Gelucire,® poloxamer 407 etc. Such a formulation, intend to produce high or supersaturated intraluminal drug concentration by increasing the drug apparent solubility. The initial degree of supersaturation is in most cases dependent on drug loading, polymeric matrix composition as well as method of preparation, while the duration of supersaturation depends on the presence of precipitation inhibiting agents in the co-dissolving with the drug polymeric matrix. HPMC has been used as polymeric matrix for the molecular dispersion of itraconazole (Sporanox®) and the solid dispersion of tacrolimus in an amorphous state. Supersaturated concentrations were maintained for 4h and 24h, respectively in biorelevant media.[6,46,47]

It is also possible to incorporate nanoparticles into the conventional solid dispersion systems. When possible, the use of nanoparticles, increase the available for dissolution surface area and enhance furthermore the apparent solubility of the poorly water soluble drug and the ability to form supersaturated solutions.

Co-ground mixtures are often used as an alternative to avoid the problem of thermodynamic instability of the amorphous-based dosage forms used to formulate poorly water-soluble drugs. In co-ground mixtures the crystalline form of the drug is used, mixed and co-grinded with pharmaceutical excipients such as lactose and HPMC. This procedure often results in limited supersaturation that may significantly increase oral bioavailability of poorly water soluble drugs.[46]

Inorganic materials, have also gain great attention as possible carriers for poorly water soluble drugs.[47,48] Recently, an ordered mesoporous silica (OMS) based delivery system of itraconazole was developed by Mellaerts et al.[49] The formulation contains molecularly dispersed itraconazole into the cylindrical pores of OMS. Supersaturated itraconazole solutions were obtained when drug release from OMS in simulated gastric fluid was studied, that remained constant for at least 4h even when dissolution medium was turned to simulated intestinal fluid.

Crystalline salt forms of weak acids and bases and pro-drugs with improved solubility and dissolution characteristics have been also used as strategies to enhance oral absorption of poorly water soluble drugs. Examples of the first case are several non-steroidal anti-inflammatory drugs, e.g. diclofenac, celecoxib, nimesulide, that are administered in the crystalline potassium or sodium salt form, being more than 90% bioavailable compared to their free acid form. However, the use of salt formation requires an ionizable group and, therefore, this is not a viable option for neutral compounds or those with ionization constants that do not fall within the physiological range.

The development of pro-drugs i.e. chemically modified versions of the pharmacologically active agent that must undergo transformation *in vivo* to release the active drug, is also a useful strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase the developability and usefulness of a potential drug.[50–52] The water-soluble oral pro-drug of the non-steroidal anti-inflammatory drug sulindac, is an example of this strategy. Sulindac is formulated as a pro-drug that contains the inactive sulphoxide form which gives the active sulphide form after oral absorption.[53,54] The sulfoxide form pro-drug, is about 100-times more water-soluble than the pharmacologically active sulphide. The greater solubility of the pro-drug in conjunction to its optimal lipo-

philicity (logP 1.52 at pH 7.4) provides more efficient oral absorption.[53,54]

Phosphate esters can increase the oral bioavailability of many poorly water-soluble drugs. They are especially useful for drug candidates that require a high dose and exhibit a dissolution-rate limited absorption.[52] Nearly all oral phosphate ester pro-drugs are rapidly hydrolyzed to the parent drug by endogenous alkaline phosphatases at the intestinal cell surface during absorption, leading to low pro-drug concentrations in the systemic circulation.

An example of water-soluble phosphate ester is fosamprenavir (Lexiva/Telzir; GlaxoSmithKline), the phosphate ester of the HIV protease inhibitor amprenavir (Agenerase; GlaxoSmithKline), which shows improved water solubility and an oral bioavailability that is equivalent or higher to that of amprenavir.[55] However, the poorly water-soluble amprenavir (0.04 mg per ml) requires a high dose (1,200 mg twice a day, or 8 capsules), while fosamprenavir has a 10-fold higher water solubility, permitting a more patient convenient dosage regimen (4 tablets once a day).[55,56] After administration, fosamprenavir is rapidly hydrolyzed to amprenavir by gut epithelial alkaline phosphatases during absorption and limited concentrations of the pro-drug reach the circulation.[56,57]

## Development of paediatric formulations: a challenging task

Since the recent adoption of Paediatric Regulations in the U.S. and E.U., there is a greater demand for age-appropriate medicines for children. Even though there is a growing demand, still paediatric drug formulation science is at the beginning. The reason why is because it is complex, multi-parametric, resource- and time-intensive. Developing such formulations is a very challenging subject. There are a lot of parameters that should be taken into account and there are still many open questions. Solid dosage forms present some issues, as children have difficulty swallowing whole solid drug carriers like tablets or capsules. Moreover, providing age-appropriate doses at different strengths is a big issue, while problems in dosing accuracy, stability, palatability and unknown bioavailability of compounded products exist in liquid forms. So, the challenges in paediatric formulation development are mostly associated with the difficulty in defining design requirements for the intended dosage form that is most appropriate for the target patient population, along with the dosage flexibility. Up to now, most medications were made for adults and children's requirements were not taken into account. There are also concerns about extemporaneous formulations, especially around lack of dose accuracy, stability and consistency in preparation.

This diversity drives the need for different formulations, based on the needs and capabilities of the target population, as well as a wide range of dosage strengths within each formulation. The difficulty in defining design requirements is mainly derived from the diversity of the population that can be encountered due to the range of ages, physical size and capabilities of the paediatric population that varies significantly from birth to age 12 yrs old.

Defining design requirements for oral dosage forms is primarily determined based on the age, size and capability of the target population to swallow different sizes of dosage forms in order to effectively achieve dosing or acceptance of the dosage form. One main issue when designing paediatric formulations is the volume of the liquid, which has to be very small, especially if administered to infants or the size of the capsule/tablet. This diversity and range of ages also drives the need for a potential large range of dosage strengths over the range of ages defined by the target patient population. When patients are over the age of 6 yrs old there is better acceptance of small to medium tablets intended for swallowing but there is at least a relatively large percentage of the population that still have difficulty swallowing tablets or capsules. When children reach the age of 12 yrs, then most patients can swallow a tablet or capsule of reasonable size. After that age the difficulties in delivering a solid oral dosage form decrease significantly and the diversity in the population in this area of design is decreased. When the age range of the target population is from birth to 8 or 10 yrs of age then the design requirements is generally complicated.

For patients below 2 yrs of age, tablets or capsules are not appropriate for swallowing as a whole dosage form. In children less than 2 yrs of age, generally liquid dosage forms are widely acceptable and in some cases orally disintegrating or film strip type dosage forms could be acceptable. Between the ages of 2 to 6 years of age the capability of a child to swallow a small size tablet or capsule is highly variable and many times based on experience. The EMA guidance states that tablets should be not larger than 5 mm for patients less than 6 yrs of age and this size can still be an issue for swallowing in many patients. In order to achieve acceptable dosing in the diverse population encountered in this age range, it is recommended that a liquid or orally disintegrating dosage form be considered.

## 'User friendly' paediatric formulations

The last years there has been an effort to develop solid paediatric formulations that deliver the appropriate dose in a "user friendly" way and to find alternative drug delivery vehicles, such as mini-tablets, dairy products, and new taste masking techniques in order to improve drug acceptability. Oral pathway is the most common route of drug administration, and a great progress has been recorded in this area concerning paediatric formulations. Pellets and generally small-sized dosage forms like mini-tablets or sprinkles are very popular solid carriers which give the flexibility to be administered alone or dispersed in food. Orodispersible drug formulations which disintegrate within few seconds in the oral cavity is a different approach of innovative dosage forms, such as oral lyophilisates, orodispersible films and orodispersible tablets (ODTs).[58] The combination of both approaches, small-sized dosage forms and orodispersible formulations, led to orodispersible mini-tablets,[59] offering numerous advantages for paediatric treatment over conventional techniques.

For newborn infants and young children (below 6 years old), liquid dosage forms are preferred instead of solid oral dosage forms, because of swallowing issues. It has been developed a modified feeding bottle (Medibottle®) which delivers the drug while the baby drinks milk or other drink. By this way can be reassured that the whole drug amount will be delivered to the baby. For the delivery of a single dose of small-sized pellets has been developed the Dose Sipping Technology. With this innovative technology children's' swallowing issues could be overcome, as small-sized pellets are incorporated in a straw and when the child holds the straw in a beverage and by sipping, the drug is delivered in a 'user friendly' way.[60] An interesting alternative drug delivery vehicle is milk. Milk, which is a natural oil-in-water emulsion, is a bio-medium familiar to infants and older children. The development of supersaturated alkaline solutions containing high concentration of acidic drugs (e.g. NSAIDs) and then dispersing them into milk is an interesting way to deliver drugs to children in a 'friendly' way.[12] Recently, another innovating formulation has been developed, such as the 'pill swallowing cup'. This cup, which contains the appropriate dose, is filled full with a beverage and then the patient drinks the drug from the cup. It helps patients who have difficulty in swallowing tablets.[61]

Measuring spoons provide the appropriate dose, for the forms that require administration with a measuring device. With this technology, the use of inappropriate devices avoiding, such as household spoons (teaspoons and tablespoons), which can lead to inaccurate dosing.[62,63] In case that larger volumes of medicine are required (more than 5 mL) then an alternative solution could be graduated measuring cups. A disadvantage of these cups is that it is likely to result in overdose due to their restricted accuracy level. It has been found that oral syringes provide more accurate results than dosing spoons[64,65] but for the correct filling of the syringe clear instructions should be provided to avoid air bubbles.

Medications that are administered via the inhaled route are preferred for respiratory diseases. The therapeutic aerosol is delivered directly to the target with less systemic side effects. However, there are numerous difficulties concerning the development of paediatric inhalers. Children's airway anatomy and inhalation pattern is very different compared to adults. This has to be taken seriously into account when it comes to the development of paediatric formulations.

Compliance is essential for therapy via the inhaled route and a close monitoring of children's inhalation technique is needed. Pressurized metered dose inhalers (pMDIs) are not appropriate for children under the age of 6 years. Breath-actuated pressurized metered dose inhalers may be a more appropriate alternative, as they have a special mechanism automatically releasing the aerosol during the inhalation, but children must be able to overcome the actuation force threshold by inhalation.

Despite the fact that ultrasonic and jet nebulizers require power and tend to be expensive are still widely used. Dry powder inhalers (DPIs) are an alternative solution to pMDIs. DPIs take advantage of the patient's peak inspiratory flow in order to deliver the drug into the system. One example is the Babyhaler which has been recently developed and it is a valve holding chamber especially designed for the use in infants. Smaller and more portable devices that have recently been developed[61] are AeroNeb® Go, MicroAir™ and I-Neb® AAD®.

When small doses of drug are required, parenteral delivery provides precise and regulated infusion rates, as in Type I diabetes. Recently, a number of needle-free drug delivery devices have been developed which deliver large molecules, such as insulin, vaccines and growth hormone, under high pressure through the skin. Such devices include J-Tip®, PharmaJet® and Bioject® delivery systems, which reduce the discomfort or the patient anxiety caused by needles. Nasal delivery is another interesting and alternative route of drug delivery. ViaNase™ and the OptiNose™ nasal delivery devices have been developed for children, although nasal formulations are mainly focused on adults.

## Conclusions

In most cases, the formulation of poorly water soluble compounds is oriented toward the creation of a supersaturated solution upon contact with aqueous environment, often combined with solubilizing agents and precipitation inhibitors. This is very effective for drugs formulated and intended for adult administration. Up to now, most medications were made for adults and children's requirements were not taken into account. However, since the recent adoption of Paediatric Regulations in the U.S. and E.U., there is a greater demand for age-appropriate medicines for children. To this end, the last years there has been an effort to develop solid paediatric formulations that deliver the appropriate dose in a "user friendly" way and to find alternative drug delivery vehicles, such as mini-tablets, dairy products, and new taste masking techniques in order to improve drug acceptability. In addition, alternative routes of administration have been proposed such as inhalation and nasal administration.

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