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Mini-Review

Orally Disintegrating Films and Mini-Tablets—Innovative Dosage Forms of Choice for Pediatric Use

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Abstract. Oral drug delivery is a non-invasive and therefore a very convenient route of administration. Orally disintegrating dosage forms, like soluble films and (mini-)tablets, appear promising for use in the pediatric population. New guidance for the development of pediatric medicines has been published, which provides considerations on how pediatric products should be designed. However, most of the considerations leave a lot of room for interpretations. Bearing in mind the different aspects discussed in the latest guideline, the use of orally disintegrating films and tablets, in particular, small-sized tablets, is discussed and reflected upon by providing evidence from the scientific literature. The available dosage forms for children are various and examples of currently licensed products for use in the pediatric population were compiled. Aspects such as the appropriateness for pediatrics, the choice of excipients, the opportunities for modified drug release preparations or fixed-dose combinations, the acceptability and palatability, and also limitations were discussed with respect to the new dosage forms of orally disintegrating films and mini-tablets. This paper points out that innovation in pediatric medicines are planned and should be encouraged; however, supported by the regulatory guidance, only general considerations are provided. Nevertheless, the guideline summarizes multiple points to consider during the development of medicines for pediatric use. Considering the scientific evidence and the regulatory guidance, orally disintegrating dosage forms, like soluble films and (mini-)tablets, offer an innovative solution for pediatric drug delivery.

KEY WORDS: children; orally disintegrating dosage forms; pediatric drug delivery; pediatrics; orodispersible films and tablets.

INTRODUCTION

The supply of age-appropriate dosage forms of drugs is a major task. With respect to certain patient populations such as children, medicinal treatment can be challenging (1,2). Esophageal diseases and swallowing issues may complicate compliance and adherence in these patients (3), who often face problems regarding the administration of their medicines. With respect to physical attributes, children in younger age groups might not be able to swallow the same size dosage forms that adults can manage. Thus, children form a vulnerable and special patient group, making it worthwhile to further develop dosage forms in order to facilitate drug administration. The challenges for accomplishing pediatric oral/oromucosal drug delivery are summarized in Table I based on the claims of Breitkreutz and Boos (1).

REGULATORY GUIDANCE: MEDICINES FOR PEDI ATRIC USE

The European Medicines Agency (EMA) recognized the need for legal guidance for the development of medicines for pediatric use. After a round table of experts by the European Commission (EC) in 1997, there was the aim to introduce new legal regulations and to provide a system of incentives. The EC supported an international discussion on clinical trials in children and an International Conference of Harmonisation (ICH) guideline was agreed in 2000. In 2002, a consultation paper on "Better medicines for children—proposed regulatory actions in paediatric medicinal products" was published by the EC, and in the following years, draft regulations on medicinal products for pediatric use were released and entered into force in 2007. The Committee for Medicinal Products for Human Use (CHMP) initiated the creation of an Expert Group on Paediatrics (PEG) to advice the EMA, which was later replaced in accordance with the pediatric regulation by the Paediatric Committee (PDCO). The PDCO mainly evaluates the data of submitted Paediatric Investigation Plans (PIPs), which are mandatory to be provided by the company upon the availability of adult pharmacokinetic data, and adopts opinions on them (4).

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Table I. Challenges in Pediatric Oral and Oromucosal Drug Therapy According to Breitkreutz and Boos

Aspects to consider
Palatability/acceptable taste
Safety of excipients
Handling of packaging
Precise and clear product information
Acceptable dose uniformity
Size of dosage form
Easy and safe administration
Sufficient bioavailability

Since 2009, all applications with a new aspect (indication, route of administration, or dosage form) must contain information and study results complying with the PIP.

Recently, a new guideline of the EMA on pharmaceutical development of medicines for pediatric use has been published and came into effect on February 15, 2014 (5). From that date onwards, adherence to the guideline is mandatory in pharmaceutical development for children between birth and 18 years of age. The aim of the "Paediatric Regulation" is to facilitate the development of age-appropriate pediatric medicines. The aim should be achieved by avoiding unnecessary clinical trials and without delays in the authorization process of medicinal products (6). The EMA, the Paediatric Committee (PDCO), and the Committee for Medicinal Products for Human Use (CHMP) do not aim to introduce restrictions, but to make guidance available.

The Food and Drug Administration (FDA) of the USA has provided regulatory framework on pediatrics since 1979, when the first pediatric labeling requirement was introduced (7). In 2010, Zisowsky *et al.* summarize the regulatory aspects of the drug development for pediatric populations of the European and US authorities. In 2001, the Best Pharmaceuticals for Children Act (BPCA) was enacted by the FDA to provide financial incentives for voluntary pediatric studies conducted by companies. The Pediatric Research Equity Act (PREA), signed into law in 2003, required that companies assess studies on safety and effectiveness of medicines in pediatric patients (8). BPCA and PREA were re-authorized in 2007 under the FDA Amendment Act (FDAAA). In 2012, amendments in the BPCA and PREA by the Food and Drug Administration Safety and Innovation Act (FDASIA) were passed and are now permanently re-authorized (9). The FDA encourages pediatric study plans to expand the knowledge and expertise in pediatrics drug therapy.

Both the FDA and the EMA released several scientific guidelines that deal with pediatric drug development in particular on considerations for the conduct of clinical trials. However, there is no such detailed guidance on formulations and dosage forms provided by the FDA like the EMA's latest publication (5). Therefore, the considerations of the latest official framework on medicines for pediatric use will be further discussed, particularly with regard to the appropriateness of orally disintegrating dosage forms.

APPROPRIATE DOSAGE FORMS

The most common solution for pediatrics may be to administer liquid formulations. The choice of formulation strongly depends on the clinical state and the age of the child. According to a reflection paper of the EMA from 2006, liquids are most appropriate for children between birth and 8 years of age, when they are unable to swallow tablets or capsules (10). The amount of liquid should, however, be as small as possible to decrease the amount of administered excipients (e.g., preservatives) and electrolytes to avoid intoxication, in particular with neonates, because of immature metabolism and elimination. Furthermore, a reduction in the amount of liquid leads to less mouth coating and thereby less potential contact and irritation to the taste buds, which can be key for a successful administration, because the smaller volume of liquid is harder to spit out. Neonates are the most vulnerable group of the pediatric population (from birth up to and including the age of 27 days). They are, moreover, treated with unauthorized and off-label medicines in almost 90% of the cases due to the lack of clinical studies, which are challenging because of multiple difficulties, such as ethical and technical issues (11). Liquids and drops seem to offer the most flexibility in dosing adjustment, according to the child's age and key factors like body weight or organ development. Nevertheless, dosing errors and stability issues are more likely to affect liquids than solid dosage forms. Dosing spoons, cups, and syringes are well-known pieces of equipment in administering medicine. However, studies revealed issues in their dosing accuracy (12–14). Palatability of liquids is key, especially when the amounts are greater than only a few drops, such as antibiotic oral suspensions, which need to be swallowed and might leave an unpleasant taste in the mouth (15).

A World Health Organization (WHO) expert forum proposed a shift of paradigm toward solid dosage forms in 2008 (16). Still, the initial situation has not changed: children are not able to swallow large-sized tablets or capsules. Even if they are able to swallow the tablet, because the child is mature enough and the physiological and anatomical prerequisites are given, they may, however, refuse the intake and/or the subsequent swallowing. Dispersible tablets, multiparticulates, and the administration of powders in sachets are not new, but there has been a resurgence of these dosage forms with the increasing awareness of what makes for successful drug therapy in pediatrics. However, a new trend in dosage form development has taken place in recent years: orodispersible tablets (ODT), which have been investigated with respect to appropriateness for children (17).

The further development of ODT has led to orally disintegrating mini-tablets (ODMT) (18). The use of small-sized tablets (1–2 mm in diameter) has been an emerging success in dosage form development. It combines the convenience of tablets, a solid dosage form, with fewer stability issues than liquid formulations present, with the opportunity to avoid child patients having to swallow a large unit, as the ODMTs are intended to disintegrate rapidly once in contact with the tongue or mucosa wet by saliva (19,20). The very small size of the tablets does not necessarily require orodispersion. Studies revealed an overall positive response of children in investigations on mini-tablet (MT) acceptance (intake and successful swallowing with the liquid of choice). The MTs (2 mm) have been favored over syrup by the children (0.5–6 years) in trials. It was found that even the very young children (6–12 months) were capable of swallowing the mini-tablet (21,22). The tendency of children to accept small-

sized dosage forms has been confirmed in a further study using 4-mm tablets compared to syrup, suspension, and powder. Parents were asked to administer placebos to their children of 1 to 4 years and rate the acceptability, and to report (non-)successful intake. The study again revealed predomination of the tablets in being the form most accepted by the children (23). More children fully swallowed the tablets than the other dosage forms. Liu *et al*. summarizes further literature reports on the ability of children to swallow tablets in relation to age and tablet size in a current review (24). The above findings demonstrate that children are willing to accept solid dosage forms; moreover, once convinced by the ease of its administration, they may even favor a certain dosage form.

The use of film preparations as an alternative to liquids or tablets is an upcoming field of interest in drug delivery. A film preparation, meaning a thin and flexible polymer sheet the size of a stamp at maximum, can be described as a solid dosage form, as the film is a solid preparation prior to administration (25). Oromucosal film preparations are placed in the mouth to disperse rapidly (orodispersible film, ODF) or are placed on the mucosal tissue and may dissolve (mucoadhesive buccal film, MBF) (26). Where ODFs may be described as an alternative oral dosage form, MBFs offer a variety of possibilities in oromucosal drug delivery.

The list of currently licensed products reveals several ODFs besides different solid oral dosage forms for pediatric use (Table II). It becomes obvious that all products licensed for use in children younger than 12 months are intended to disperse, disintegrate, or dissolve in the mouth (chewable tablet, ODF, or ODT), or need the constitution of a suspension or solution prior to administration.

DISCUSSION

Choice of Dosage Form

The general considerations given in the new guideline point out once more that the dosage form should enable the administration of variable doses and be suitable for a large range of age groups and their special needs (5). Furthermore, it becomes evident that the authors of the EMA guideline also kept in mind the competence of the caregivers of children, who are responsible for carrying out the drug administration. To choose the appropriate dosage form, the properties of the active substance should be taken into account to ensure stability. Most certainly, risks regarding dosing errors or measuring devices should be considered.

It is stated in the guideline that the use of either solid or liquid dosage forms reveals advantages. Solid, single-unit dosage forms represent an easy dosage approach. However, multiparticulates and liquid preparations may allow even more flexible dosage. An interesting statement in the guideline is the demand for investigating and developing a minimum number of dosage forms that are suitable to administer a wide range of doses for different ages, and to be able to serve the diversity of preferences. Depending on their experiences, children might refuse a certain dosage form; e.g., the child may have experienced a very poor tasting medicine in liquid form and will therefore reject all liquids. Another child may have had the same experience with tablets.

The guideline further refers to preparations that are intended to stay in the mouth for a certain length of time; the ability of the dosage form to adhere to a specific site in the mouth should also be considered. The use of ODFs would circumvent the challenge of correct use as mentioned in the guideline (e.g., measuring devices for liquids): simple placing in the mouth and subsequent immediate disintegration of the thin filmstrip does not require the application of the film to a special absorption site. The child would have nothing to accomplish other than the natural swallowing of its saliva, where the film is dispersed (27,28).

The dosing frequency is recommended to be at a maximum of two times daily with regard to the background that the medicine shall be taken at home in the morning and in the evening. More doses spread over the day would imply ease of administration that does not require the help of a trained caregiver. Some medication regimens require multiple daily doses, which challenge patients and caregivers; an easy and convenient mode of administration could therefore be beneficial to avoid missed doses (12).

Table III gives an overview on the challenges of pediatrics drug delivery showing the claims according to the latest regulatory guideline on the development of medicinal products for pediatric use. Advantages and limitations with respect to orally disintegrating film and small-sized tablet preparations are summarized in the table including references supporting specific aspect.

Modified Release

Modified release preparations are reasonable not only in terms of oral dosage forms. The advantage of prolonged release drug formulation is a reduction of the dosing frequency facilitating the therapy (5). However, the use of such preparations may entail the risk of varying efficacy, for example, when the dosage form is intended to be swallowed or remains in the mouth. The drug release may be influenced by the child chewing on the medicinal product or altering dissolution effects in the child's gastric area. In particular, children with mature primary teeth may chew the product prior to swallowing (22), which can be considered unproblematic for uncoated immediate release dosage forms under certain circumstances, but can cause problems for other dosage forms, e.g., enteric-coated tablets. Furthermore, the gastrointestinal transit times in children are highly variable (1); a modified release preparations might therefore not follow the expected release kinetic (47).

Modified release preparations could be obtained by coating drug particles or drug-loaded granules prior to incorporation in film preparations or prior to compression to orally disintegrating tablets. Mucoadhesive films with slowly eroding matrices offer multiple opportunities to deliver a drug in the oral cavity over a certain time, or into and through the oral mucosa, when the drug permeability is given (28). To administer the film onto a specific site in the oral cavity, a suitable applicator system might be reasonable. In addition, the adhesive properties of the film need to be ensured; unfortunately, there is no adequate or standardized method provided so far, which allows determining and assessing the adhesion of oromucosal dosage forms (48).

Table II. Examples of Licensed Oral Dosage Forms for Pediatric Use

Dosage form	Age	Active ingredient	Comment	Supplier
Solids				
Capsules	≥6 years	Methylphenidate	SODAS® (Spheroidal Oral Drug Absorption System) technology, 50% IR beads, 50% enteric coated, DR	Ritalin LA® (Novartis)
Chewable tablet	>6 months	Montelukast		Singulair® 4-mg chewable tablets (Merck Sharp and Dohme)
	>2 years	Cetirizine		Zyrtec® chewable tablets (Pfizer)
	<6 years	Carbamazepine		Tegretol® (Novartis)
Chewing gum	≥6 years	Dimenhydrinate		Superpep® travel gum (Hermes)
	≥2 years	Simethicone		Pedia Lax® (Fleet)
Microcapsules/ -spheres	>1 year	Ciprofloxacin	Constitution to a suspension	Cipro® Bayer
	>3 months	Cefuroxime	Stearic acid-coated microspheres: taste-masking and drug release in lower GIT	Ceftin® (GlaxoSmithKline)
ODF	≥0.5 years	Ondansetron		Setofilm® (APR and Labtec and Monosol Rx)
	≥2 years	Sennosides		Pedia Lax® (Fleet)
	≥4 years	Diphenhydramine/ Phenylephrine		Triaminic® Thin Strips™ cold and cough (Novartis)
ODT/melting tablet	≥6 years (2 years; 0.5 months*)	Prednisolone		Orapred® ODT (Concordia Inc.)
	>2 years	Ondansetron		Ondansetron ratiopharm® ODT
	≥6 years	Ibuprofen		Nurofen® (Reckitt Benckiser)
	>6 years	Desloratadine		Clarinex® (GlaxoSmithKline)
	>1 year	Lansoprazole	Delayed-release ODT (e.g., suspended in oral syringe)	Prevacid® (Takeda)
Sprinkle capsules	≥2 years	Topiramat		Topamax® (Janssen-Cilag)
	>1 year	Lansoprazole	Delayed-release granules	Prevacid® (Takeda)
Tablet	≥6 years	Ibuprofen		IBU-ratiopharm® (Ratiopharm)
	≥6 years	Sertraline	Scored tablet	Zoloft® (Pfizer)
Liquids				
Suspension/ solutions	> birth**	Antibiotics, e.g., amoxicillin	Constitution to a suspension	Multiple suppliers
		Glucose/electrolytes	Mixture to be dissolved in water	Oralpädon® (Stada)

IR instant release, *DR* delayed release, *GIT* gastrointestinal tract, *ODT* orodispersible tablets
*Cautious use only
**"From full-term birth and for pre-term neonates who are able to swallow and accept enteral feeding" (16)

Fixed-Dose Combinations

Combination drug products are advantageous in the treatment of chronic diseases (e.g., HIV, tuberculosis). The development of age-appropriate fixed-dose combinations is encouraged by the European Medicines Agency (5). However, flexibility and adequate dose adjustment needs to be ensured. Splitting fixed-dose combination (FDC) tablets showed irregularities in dose uniformity (38). The dose of the single active substances in a FDC might not be suitable for all age

Table III. Aspects Supporting or Limiting the Use of Orally Disintegrating Films and Mini-Tablets in Pediatrics

Challenge	Regulatory claims (EMA guideline)	Orally disintegrating film and mini-tablet preparations		
		Advantages	Limitations	Scientific reference/supported by
Size of dosage form	Children may not be able or willing to swallow a medicinal product/infants are simply unable to swallow conventionallysized tablets	Orodispersion Jelly behavior of polymer film facilitates swallowing	Non dispersion due to low amounts of saliva	2-mm mini-tablets (0.5–6 years) (21,22) 3-mm mini-tablets (2–6 years), derived recommendation: ≥4 years (29) 4-mm tablets used in food supplements (30) Facilitation of swallowing by using a cup system (31) or instant gelation of film layer (32)
Taste of the active substance	Overcoming taste issues: e.g., improved solubility (use of salt or different salt instead of base) e.g., less soluble form, e.g., base instead of salt	Fast disintegration, swallowing with saliva, minimal mouth coating compared to liquids Coated or insoluble drug particles can be swallowed after disintegration of the dosage form	Suitability of taste-masking agents (safety aspects, acceptable daily intake levels) Limited drug load/ Decreased drug load depending on taste-masking strategy	Less soluble APIs: taste of suspension accepted compared to placebo (33) Less bitterness of less soluble base (34) Free acid is more palatable than salt (35,36)
Oral administration	Solid single-unit dosage form: stable and easy dosing approach Dosing flexibility: greater for oral powders, granules, and liquids than for oral solid single-unit dosage forms Liquids: avoiding multiple step procedures (risk of dosing errors)	See EMA claim Dosing flexibility of mini-tablets No need to split large tablets Dose by film size	Multiple dosing might be necessary	Mini-tablets (17,18) ODFs prepared on a small scale for individual dosing (17,18,37) Content variation in split tablets (38)
Dosing frequency	Preferred: maximum of twice daily dosing Special attention when medicines used more than twice daily (suitability of administration when no trained caregiver is around, e.g., in day care or school)	Ease of administration/ administration on demand No special training needed Flexibility of dosage form enables tailoring the medication regimen to the child's daily routine	Multiple dosing might be necessary due to the limited drug load per single unit	Adherence to multiple dose regimen (39,40)
Measuring device Risk of dosing errors	Ensure the ease and accuracy of the administration Oral liquids: oral syringe should be more readily considered in the youngest age groups than a spoon or a cup	No liquid dosing device such as cups or syringe needed Lower risk of dose dumping	No multiple step procedure for liquids compared to the intake of multiple films/tablets to administer the required dose	Suitability of the graduation of delivery devices (14,41,42) Accuracy of dosing devices (14) Parents' accuracy in using dosing devices for liquids (12)
Excipients	Key element of the development Special safety considerations for children	Film-forming polymer material is widely used e.g., for other pharmaceutical coating processes Known tableting excipients	Choice of solvent in film preparations Suitability of taste-masking agents	Safety and toxicity considerations on taste-masking agents and coating materials (43) Influence on bioavailability (44) Careful use of solvents and sweeteners (45) Issues relating to the risk assessment of excipients in neonates (46)

groups, so there would be the need for several combinations. In a specific case, younger children with low body weights had subtherapeutic levels of one drug after receiving a FDC, which was explained by increased metabolism for the specific drug (49). Small-sized orally disintegrating tablets could be combined to provide accurate dose combinations to children of different age groups.

The provision of tailor-made FDCs can be facilitated by using oral film preparations, which can be prepared on demand in small scales (37). Innovative technologies such as printing approaches to oral film preparations enable highly flexible dosing and dose combinations (50–53).

Acceptability and Palatability

The acceptability of medicinal products for children is highly dependent on individual conditions, such as the patient's age, mental state, how familiar the child is with a particular treatment, co-medications, or the duration of the treatment (54). However, there are aspects like the taste of the API, the overall palatability, dose regimen, and mode of administration that can nonetheless influence acceptability. It is stated in the EMA guideline that an international harmonized method for assessing acceptability is lacking and that the authorities know about variation in the outcome of acceptability trials even when same target groups are investigated. However, when discussed thoroughly, it becomes evident that reasonable benefit-risk consideration may justify the chosen method. The EMA collaborator Kozarevicz provides an overview of critical attributes, which should be considered in acceptability testing and encourages a wider discussion to obtain a harmonized worldwide approach to confirm acceptability (54).

A major acceptance criterion is palatability, which can be described as the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste, and texture. Palatability is mainly influenced by the characteristics of the active substance and excipients. The guidance points out that information on the palatability of the active substance should consequently be acquired at an early stage in the development of a medicinal product, e.g., from dedicated adult panels or literature (5). The assessment of results from human taste panels and the acquisition of literature on the taste of specific active substances is a major challenge. Furthermore, the taste perceived by adults may significantly differ from the perception of children (55,56). The use of visual scaling systems to rate samples in sensory panels is a reasonable approach, which could also be used in trials with children, but younger children may be more likely to choose extremes (e.g., very good or very bad), and the appearance, e.g., the color of a presented sample may influence the overall acceptability (57). However, taste assessments at an early stage in development are stated to be important. The use of electronic tongues is an innovative approach to circumvent taste panels to investigate formulations, and to provide pre-selection for further trials before having to employ cost-intensive human trials (58–60).

The mixing of drugs with food and drinks is accepted as reasonable in terms of masking the taste and insufficient palatability, when a formulation does not provide acceptable palatability and when the taste could not be improved in other ways. Therefore, effects concerning the mixing with food and drinks should be discussed for a novel formulation with regard to feasibility, stability, and compatibility. Even though the product is considered having an acceptable taste, caregivers might consider the use of food to facilitate the administration (61). Therefore, the manufacturer is advised to provide information about suitable food and drinks that do not influence the quality and effectiveness of the medicinal product.

With an orally disintegrating dosage form, taste is a major challenge. The dosage form remains in the mouth for a certain time while disintegrating. The child might not be able to spit out an unpleasant tasting product due to the immediate dispersion. However, it is not expedient to neglect the taste properties over the ease of administration and rapid dispersion since the child would more than likely refuse future doses. Therefore, during the development of a child-appropriate medicinal product, measures have to be taken to mask the poor taste of the active substance or to improve the taste of the formulation (62).

Excipients

The choice of excipients is another crucial factor in the development of medicinal products for pediatric use. The EMA guideline provides a decision tool to evaluate the safety profile of excipients. The easiest way to ensure that an excipient can be used is to consult a European Food Safety Agency (EFSA) scientific opinion available for the excipient supporting its use in children's medicine. Unfortunately, the food opinions do not always cover neonates. There is a tremendous need for a systematic approach in particular to assess the risk of neonatal excipient exposure (46).

According to the guideline (5), justification to use a particular excipient can be given when the safety profile of the excipient can be assessed by consulting the information listed in the following hierarchy:

– Commission, ICH, and EMA guidelines
– Included in a CHMP scientific opinion or
– Authorized in current pediatric medicines with known quantitative composition or
– Included in the European food legislation
– Included in EFSA opinions
– Other sources such as the expert committee on food additives (JECFA), indexed literature, or in-house scientific evidence

The information must be still up-to-date, related to the target age group, and relevant to the maximum daily exposure/acceptable daily intake (ADI). Unfortunately, these designated sources do not always provide the information needed in particular with regard to children. European and US Pediatric Formulations Initiatives (EU-US PFI) are working on a Safety and Toxicity of Excipients for Paediatrics (STEP) database of practical use (43).

If none of this information is available on the particular excipient, additional data is required, e.g., juvenile animal/clinical studies, or there is simply the need to reformulate and choose other excipients. The acquisition of the required additional data is connected to high costs and is not affordable for most suppliers. Consequently, nobody wants to introduce a novel excipient that has not been described previously elsewhere and will therefore consider reformulation and exclusion

of the excipient. The excipients used for orally disintegrating films and mini-tablets are not new in most cases. However, attention is to be paid to excipients such as solvents, plasticizers, coloring agents, or preservatives. The need for acceptable, and in particular palatable, formulations for children makes the use excipients to mask or improve the taste of the drug inevitable, but also requires careful evaluation of the used substances (62).

Limitations

There is a limitation on drug load in oral films and mini-tablets; with respect to pediatrics, however, lower, and more important flexible doses are required in most cases, especially for neonates. Depending on the mini-tablet's diameter, the MTs may weigh only 6 mg (18), which limits the drug load capacity per tablet. Higher drug loads in films might lead to increased thickness and slower disintegration and require individual evaluations with respect to their suitability. However, drug loads up to 62.5 mg (GasX® Thin Strips, Novartis, USA) can be considered per single dose depending on the active ingredient properties and film size. Careful evaluation is required when it comes to sustained release preparations. Coatings of drug-loaded granules may rupture during processing or chewing, which may influence the release properties and the taste-masking effect.

CONCLUSION

The overall impression of the new guidance is that the authorities possess an immense interest in improving and promoting the development of pediatric medicines by providing considerations on how new products should be designed. Additionally, the guideline implies that innovations in pediatric medicines are intended and should be encouraged. Nevertheless, scientific evidence of the suitability of dosage forms and excipients for certain age groups, in particular, for very young children, is only available to a limited extend. This is due to a lack of guidance when it comes to acceptability testing and the special challenge of assessing data in the pediatric population.

With respect to crucial aspects in the development of medicinal products for pediatric use, orally disintegrating or dissolving films and tablets, in particular, mini-tablets, offer a promising solution for successful pediatric drug therapy. The ease of administration and the minimized risk of choking on these small-sized products—potentially combined with considerably fast disintegration directly in the mouth—lead to the conclusion that these dosage forms may become the products of choice for pediatric use. Clinical trials in children with oral films are not available at this point, but recent studies confirmed the suitability of small-sized tablets even in very young children. It became obvious that caregivers and children acknowledge the convenience of solid dosage forms. However, there are limitations such as a limited drug load. If future studies could reveal the acceptability of multiple dosing approaches, this could pave the way for higher variability in dosing. Moreover, if the suitability for neonates could be shown in the future, orally disintegrating dosage forms may be the innovative solution for oral pediatric drug delivery in all age groups.

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