Paediatric and geriatric drug delivery

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Age-adapted drug formulations are a challenge in drug development. This paper describes the special requirements of paediatric and geriatric patients, and new ideas to solve the most prominent problems in the application of drugs to these patients. Most requirements are very similar in each subpopulation, but there are also some particularities. In neonates and infants, the immaturity of enzymes may determine the pharmacokinetics of the excipients, which must be carefully selected. Pharmacokinetics in the elderly are strongly influenced by co-morbidity, multiple-drug use or reduced organ functions. The drug handling and the readability of the product information are key issues in both subpopulations. Children and the elderly show difficulties in swallowing solid dosage forms for oral use. In both patient groups, small sized particulates or liquid dosage forms are superior to classic tablets or capsules. The main problem with using liquids is the palatability of the solution, especially when considering that taste sensation differs age-dependently and interindividually. Recent technological developments such as the dose sipping technology, promise improvements. The new EU legislation for the development of new paediatric drugs may also stimulate the research into drug delivery for the elderly.

Keywords: application devices, individual dosing, multiple-unit dosage forms

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1. Introduction

When prescribing a drug, a physician has to consider whether the patient is able to receive the drug dose completely, safely and comfortably. A critical review of the available products shows that this is hardly the case for most drug products used in the paediatric and geriatric subpopulations. The issues of site of application, dosage form, composition of the formulation and the method or route of administration need careful consideration. Paediatric and geriatric patients differ in many aspects from a 'standard patient,' who is the focus of pharmaceutical companies when they are developing new drug products. Evidence-based studies on safety and efficacy have not been conducted for most drugs in these vulnerable subpopulations. There are a number of similarities in drug delivery issues concerning the young and the elderly populations, but there are also some particularities [1]. Physiological deviations from 'normal' are most pronounced in very young and very old patients. The special attributes and conditions of paediatric and geriatric patients require appropriate drug formulations for clinical investigations and for marketed drugs [2].

The paediatric population is divided, by age, into five or six categories. In the 'Note for guidance on clinical investigation of medicinal products in the paediatric population' of the International Conference of Harmonization (ICH), the groups of preterm newborns, newborns, infants and toddlers, children and adolescents have been defined (Figure 1) [3]. The categorisation into these subpopulations has been mainly derived from physiological and pharmacokinetic differences (e.g., metabolic capacity, organ maturation and drug clearance) [4]. Differences in the metabolic

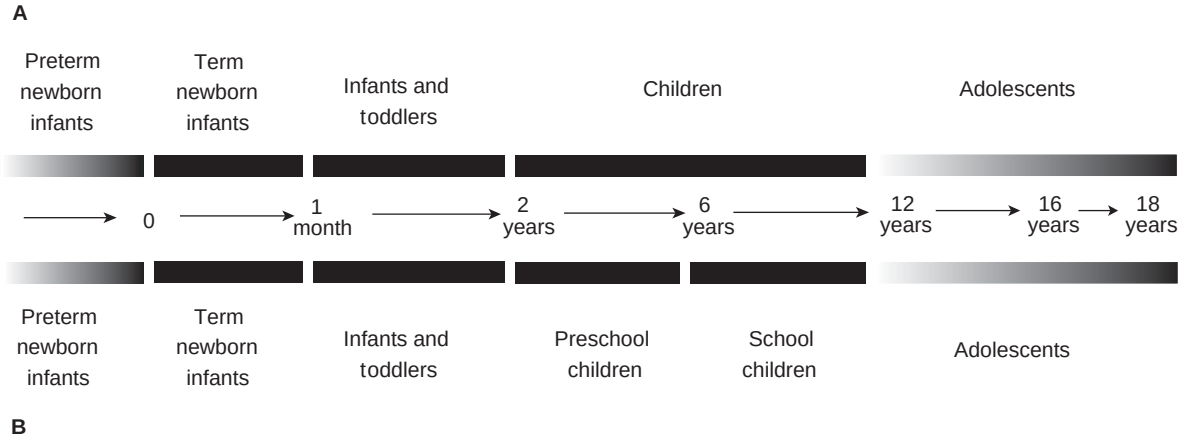

Figure 1. Age categorisation of children according to current EU guidelines and opinions.
A. Information from [3].
B: Information from [6].

pattern can be observed, especially in the the first 6 months after birth, when compared with older children and adults [5]. Treatment failure and toxicity may result if the drug dose is not adequately adapted. The European Committee for Medicinal Products for Human Use (CHMP) has recently released a paper that splits the group of 'children' (of the ICH guidelines, ranging 2 – 11 years of age) into two subgroups; preschool children between 2 and 5 years of age, and school-going children between 6 and 11 years of age [6]. This subdivision is based on practical experience and recently published data on prescribed dosage forms in the Netherlands. The data states that starting approximately at the age of 6 years, the majority of children receive solid dosage forms for peroral drug administration, whereas liquid formulations are predominantly used below the age of 6 years [7].

Establishing age classes for drug development is impossible for geriatric patients. In contrast to children, the demands of the elderly are not closely related to age, but to the ability of the patient, which is mainly determined by the individual state of health. Many geriatric patients suffer from various diseases with multiple-drug treatment. Some of these patients are addicted to alcohol, nicotine and pharmaceuticals. Reduced kidney and liver functions as well as dehydration may dramatically alter the pharmacokinetic properties of a drug. Limited audiovisual and ergonomic abilities of geriatric patients must be assumed and considered in drug development. Unfortunately, a poor hygienic status can be expected in the domestic environment of some elderly patients, which may also influence the choice of the drug formulation. Therefore, the derivation of a 'biological' or 'functional' age has been proposed. However, this is difficult to define and to establish [1].

Many paediatric and geriatric patients depend on the abilities of their caregivers. Therefore, drugs that are patient-adapted should be designed appropriately for caregivers as well. In general, poor compliance must be expected in both groups of patients when administering usual drug formulations. Some obstacles and limitations can be overcome by new techniques and developments in pharmaceutical technology [8-10]. Although the lack of paediatric drug formulations has been described by various authors [11,12] and the term 'therapeutic orphans' (established by Shirkey H in 1968 [13]) has often been quoted, the geriatric situation and the related specific requirements for drug formulations are rarely addressed. In this paper, the persistent lack of formulations and innovative pharmaceutical products for both the paediatric and geriatric populations is presented.

2. General requirements for age-appropriate formulations

Most of the requirements for optimal drug delivery are applicable to both paediatric and geriatric patients. The desired general properties of drug formulations for both subpopulations are listed in Box 1. Accordance with the required criteria should be checked at each step of drug development.

2.1 Bioavailability/routes of administration

The bioavailability of active substances strongly depends on the properties of the absorption site, the route of administration and the properties of the drug formulation. The special conditions in children or the elderly may influence the bioavailability of a drug. Certainly, the best bioavailability is desired for each drug formulation. However, this cannot be achieved in many specific cases. The predominant route for drug administration is still the peroral route, despite its general limitations of incomplete intestinal drug absorption, varying gastrointestinal transit times, changing pH conditions along the gastrointestinal tract, drug–food interactions, first-pass effect and potential drug

Box 1. Basic criteria for both paediatric and geriatric drug formulations.

- Sufficient bioavailability
- Safe excipients
- Palatable and/or acceptable properties
- Acceptable dose uniformity
- Easy and safe administration
- Socio-cultural acceptability
- Precise and clear product information

instability in gastrointestinal fluids. Furthermore, some special conditions in paediatric and geriatric subpopulations are to be considered. In neonates and infants up to 1 year of age, the gastric fluid shows pH values of 5 – 7 in the fastened state instead of the normal range of pH 1 – 2. Enteric coatings of drugs are therefore inappropriate for this age group as the drug would be released within the stomach. In young children, and elderly patients, the gastrointestinal transit time may be highly variable due to the deviating nutrition and movement skills of these groups. Although this fact is accepted as common and non-pathogenic in newborns and infants, some elderly patients regularly use laxatives to combat constipation, which may influence the drug absorption, and hence, the pharmacokinetic profile of the co-administered drug. Additionally, chronic abuse of laxatives may have altered the enterocytes in the intestine and the drug absorption conditions.

The rectal drug-administration pathway may be used as an alternative route, especially in young children and elderly patients with special disorders, such as epileptic diseases. Advantages of the rectal route are the applicability of non-palatable drugs and the possibility to administer drugs to patients lacking compliance or consciousness. However, the bioavailability of most drugs is very limited following rectal administration. The rectal absorption site shows a minor absorption area, a lack of active drug transporters and a very limited fluid volume for dissolving the drug. Therefore, important drug substances such as levodopa, phenytoin or penicillins, cannot be rectally administered. An additional drawback is uncontrolled defecation, observed in most children and some adults, which can reduce the bioavailability of the drug. Objections to rectal applications are raised in some countries due to ethical reasons, especially by some ethnical groups or religious communities. Whereas the use of suppositories in children is quite popular in Western Europe (e.g., in Germany, France or Spain), it is uncommon in the UK or the US. Therefore, the frequency of use and the experiences of physicians with rectal drug administrations may differ significantly in each country.

The buccal administration of drugs has recently gained increased interest due to novel drug-dosage forms and more palatable drug formulations (see Section 2.3). However, one should be aware that the bioavailability of buccally administered drugs is composed of transmucosal drug permeation in the mouth and intestinal absorption after swallowing the drug-containing saliva. Hence, the pharmacokinetic profile of a drug can vary interindividually as well as intraindividually. New dosage forms like mucoadhesive films or tablets may overcome these obstacles in the future. However, the number of drugs that are buccally absorbed is limited as in the case of rectal drug administration.

The transdermal route of drug administration is even more restricted to a small number of appropriate active substances. In the paediatric and geriatric populations, the varying hydration status of the skin is a major problem that can affect drug permeation. In childhood, the water content changes significantly due to mainly metabolic or anabolic periods during development. In many elderly patients, the skin is dehydrated because of an insufficient fluid ingestion, diabetic condition or a diuretic drug therapy. When administering drugs to these patients transdermally, the pharmacokinetic profiles cannot be foreseen. The use of transdermal scopolamine patches had to be restricted to older children due to hallucinogenic reactions caused by unexpected elevated plasma concentrations [14]. However, some transdermal patches (e.g., for patches for pain relief) are widely used in the paediatric and geriatric population.

An increasingly popular method is the nasal route of drug administration. Nasal preparations (drops or ointments) have been widely used for several years, and the excellent nasal transmucosal bioavailability offers some potential, especially for non-compliant patients from paediatric and geriatric groups.

The reduced motor abilities and low inspiration volume of paediatric and geriatric patients often limit the proper use of drugs and dosage forms for inhalation. Appropriate inhalation devices are rare, but facemasks and spacers may improve the inhaled dose. When patients change their devices, it is important to realise that they may receive a very different dose [15].

If compliance is lacking because of the age or the condition of the patient, parenteral administration of drugs is still the major route. Main (potential) drawbacks of this are the hyperosmolarity of infusions [16], the clinical need to reduce the fluid uptake, plasticizer desorption from the circuits, namely phthalates, drug migration into the plastic tubes, the lag time, volume, and the punctuation pain or needle phobia of the patient [17,18].

2.2 Excipients

In general, pharmaceutical excipients, the so-called 'inactive ingredients', are safe for use in humans. The toxicity of excipients is estimated by risk assessment using cultured cell and animal models. The 'no observed effect level' (NOEL) is determined in at least three animal species. The 'Acceptable daily intake' (ADI) that is established by the Joint Expert Committee on Food Additives, divides NOEL by safety factors, reflecting the differences between the tested animals and humans and the interindividual variation within the same species. ADI values are measured as daily-tolerated mass of excipient per unit body weight (in mg/kg/day). A similar approach is the estimation of

Table 1. Excipients with elevated toxicological risk for subpopulations of paediatric and geriatric patients.

Excipient	Administration	Adverse reaction
Preterm and term neonates, infants < 6 months of age		
Benzyl alcohol	Oral, parenteral	Neurotoxicity, metabolic acidosis
Ethanol	Oral, parenteral	Neurotoxicity
Polyethylene glycol	Parenteral	Metabolic acidosis
Polysorbate 20 and 80	Parenteral	Liver and kidney failure
Propylene glycol	Oral, parenteral	Seizures, neurotoxicity, hyperosmolarity
Patients with reduced kidney function		
Aluminium salts	Oral, parenteral	Encephalopathy, microcytic anaemia, osteodystrophy
Polyethylene glycol	Parenteral	Metabolic acidosis
Propylene glycol	Oral, parenteral	Neurotoxicity, hyperosmolarity
Hypersensitive patients		
Azo dyes	Oral	Urticaria, bronchoconstriction, angioedema
Benzalkonium chloride	Oral, nasal, ocular	Bronchoconstriction
Chlorocresol	Parenteral	Anaphylactic reactions
Dextran	Parenteral	Anaphylactic reactions
Macrogolglycerol-ricinoleate	Parenteral	Anaphylactic reactions
Parabens	Oral, parenteral, ocular, topical	Allergies, contact dermatitis
Sorbic acid	Topical	Contact dermatitis (rarely)
Starches	Oral	Gluten-induced celiac disease
Sulfites, bisulfites	Oral, parenteral	Asthma attacks, rashes, abdominal upset
Wool wax	Topical	Contact dermatitis, urticaria
Patients with metabolic disorders		
Aspartame	Oral	Phenylketonuria
Fructose	Oral, parenteral	Hereditary fructose intolerance
Lactose	Oral	Lactose intolerance, diarrhoea
Sorbitol	Oral	Hereditary fructose intolerance
Sucrose	Oral, parenteral	Hereditary fructose intolerance

the 'Permitted daily exposure' (PDE) that has been established for solvent residuals by the ICH. Both ADI and PDE are commonly used for risk assessment of excipients in drugs. However, the paediatric and the geriatric populations show particular differences from the 'normal' adult patient, and this should also be considered in the choice of excipients. Major problems with pharmaceutical excipients have been reported for benzalkonium chloride, benzyl alcohol, dyes, propylene glycol and sulfites [19].

The toxicity of excipients in children is mainly attributed to the insufficient metabolic capacity in the first months of life. Deaths of neonates and low-weight infants up to the age of 6 months and severe, adverse drug reactions, such as seizures and plasma hyperosmolarity, have been reported for propylene glycol [20,21]. Propylene glycol is commonly used as a solvent or a co-solvent in drugs. It shows antimicrobial activity, which is an important property because preservatives can be avoided in these formulations. However, the metabolism of propylene glycol is poor and the substance passes the blood–brain barrier in the first months of age. Therefore, it must be used with caution. Benzyl alcohol is another dangerous excipient for neonates and infants. It is used as a solvent and preservative in drug solutions. Benzyl alcohol has caused deaths in neonates and severe adverse-effects (known as the 'Gasping syndrome') in children that involves a severe ion gap metabolic acidosis, seizures, encephalopathy, renal dysfunction and death [22]. The insufficient oxidation of benzyl alcohol to benzoic acid, and the poor capacity of conjugating benzoic acid with glycine, increase the plasma concentrations and causes fatalities [23].

Other toxic ingredients are sulfites, and may cause allergies, asthmatic attacks, rashes and abdominal upset [101]. In patients with reduced kidney functions, aluminium containing salts or substances may accumulate and cause toxic reactions [24]. Additional excipients at risk are given in Table 1.

Most excipients with toxicological risks are used for liquid drug formulations. Solid drug formulations can usually be composed using non-toxic ingredients. However, liquid drugs offer some practical advantages in dose adaption (see Section 2.4) and drug administration (see Section 2.5). Therefore, the best formulation must be carefully chosen taking many factors into account.

2.3 Acceptability and palatability

According to a Danish study, ~ 50% of parents report difficulties in feeding liquid or solid formulations orally to their children [25]. The main problems were the taste and the swallowing of solid dosage forms like tablets or capsules. The difficulties were more pronounced among neonates and infants. Neonates and infants react adversely to bitter and salty tastes. According to the prescription data from the Netherlands, in the subpopulation of children up to 6 years of age, liquid formulations dominate [7]. However, if there is no alternative, solid formulations seem to be an appropriate formulation, as indicated by the deviating curves for the off-label use in the same study. It is the authors' experience that small-sized pellets, when mixed with food or juices, are well accepted by infants from the age of 3 months onwards. It has also been reported that preschool children are able to swallow large tablets, and can also swallow a huge number of different tablets (in a study for the treatment of their HIV infection, after a training program) [26]. Approximately 50% of the children were able to continue the therapy with solid dosage forms after the teaching period.

The CHMP paper categorizes powders and multiparticles into class 2 (out of 5) for the term newborn infants, infants and toddlers [3]. This means that multiparticulate formulations would only be 'applicable with problems'. These recommendations of the paper seem to be very restrictive, and do not reflect our practical experiences. In practice, multi-particulates dispersed in liquid or semi-solid material, such as cream or pudding, are administered to children at the age of 6 months. Certainly, this is more difficult in younger children than in the older ones, but sometimes it is more comfortable than the administration of a liquid preparation with an unpleasant taste.

The development of liquid formulations is limited by the poor stability of various drugs in aqueous solutions and the use of preservatives (see Section 2.2) that are required for most liquids in multiple-dose containers. Additionally, there are only few opportunities to mask the taste of the drug substance in liquid formulations. If the drug has a pronounced bitter taste, there is hardly any possibility to mask that taste. In these cases, solid multiparticulates coated with taste-masking films are the formulations of choice. Different formulations for sodium benzoate, a preservative used at very high doses of up to 12 g/day, have been developed for some rare metabolic diseases [27]. Liquid formulations of the bitter and salty drug are not palatable, but the developed saliva-resistant pellets are fully accepted by almost all children receiving the new formulation. The youngest patient initiated the therapy at the age of 3 months.

Taste may also be influenced by disease. Some patients receiving cytostatic agents lose their sense of taste to an extent, and can be treated better in disease conditions, with non-palatable liquids than in healthy conditions. In human development of taste, sensation changes, and at an older age, some taste may be completely lost.

2.4 Dose adaptation

A key problem is the accuracy of dosing. Whereas the dose in liquid formulations may be easily adjusted by volume determination, splitting of tablets is more complicated and less accurate [28]. Many solid formulations exhibit special drug-release characteristics (e.g., saliva-resistant, enteric-coated, sustained-release and colonic targeting formulations). Some tablets are monolithic, and others contain multi-particulates that can be coated with functional polymers. Improved tablet geometries such as the 'Snap-Tab™' principle diminish powder loss when breaking tablets, and ensure dose uniformity of the tablet segments [29]. There are various instruments to facilitate the splitting of conventional tablets. However, the splitting aids do not usually improve the dose uniformity of the produced segments, and therefore, may not replace the development of appropriate formulations.

Tablets with multiparticulates can be split into segments without losing the drug release principle in most cases. By simply reading the labeling of the product, even experts can often not elucidate whether the tablet may be split or not. If tablets are split into pieces, drug-containing dust is produced. Splitting tablets that contain cytotoxic, mutagenic and reproduction-toxic substances, results in the contamination of the domestic environment with hazardous dust [30]. Therefore, novel formulations with doses appropriate for all patient subpopulations are urgently needed, at least for the cytotoxic, mutagenic and reproduction-toxic substance-containing drugs. New technologies for the formulation of solid drug dosage forms offer some new possibilities. Advanced multiparticulate systems are pellets, micropellets and minitablets that can be used to cover a broad range of doses for different patients. A complete hard capsule that is filled with microparticulates can be administered to an adolescent or an adult, whereas a single pellet or minitablet inside the capsule shell can be used for infants or elderly patients with swallowing deficiencies. In our experiences, solid multiparticulates can be administered at an earlier stage of development than stated by the EMEA reflection paper (see Section 2.5). Improved devices such as multiparticulate counting devices and tablet pens could be further options in the future [10].

Recent studies indicate that the dose adaption from liquid drug formulations is not as easy as formerly expected. The delivered dose from a multiple-dose container is only accurate if the dropper is held vertically when using central dropper inlets for drug solutions. If patients have been

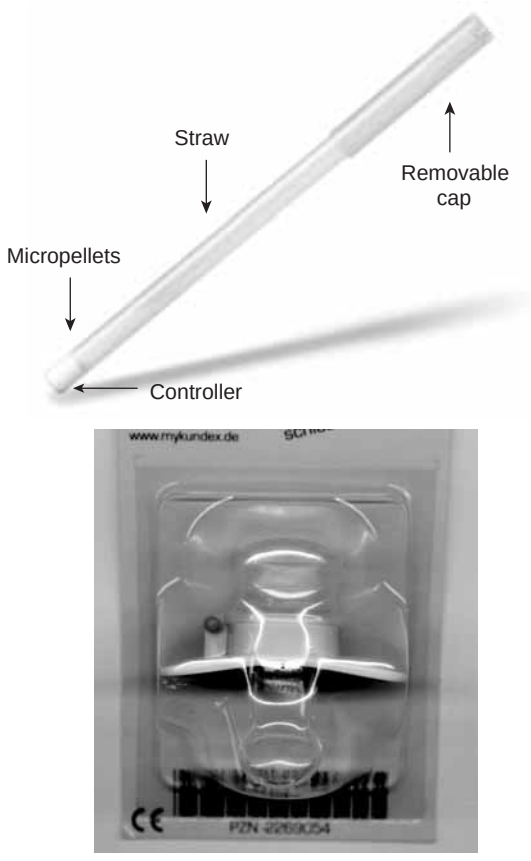

Figure 2. Special application devices for improved drug admininistration to childred. A. Dose sipping technology (DST): straw containing film-coated clarithromycin pellets (Clarosip™, Grünenthan). B. Drug-loaded pacifier for constant delivery of nystatin into the oral cavity (Mykundex™, Bioglan).

thoroughly instructed by the pharmacist, the uniformity of the delivered doses is improved [31]. An improved primary package is the dropper tube used for codeine drops (e.g., Paracodin™). The dropper tube delivers equal drop volumes at every position, and hence ensures dose uniformity. When administering liquid formulations with measuring devices such as dosing spoons or dosing cups, surprisingly poor dose uniformity was demonstrated for amoxicillin formulations at lower volumes, due to the high surface tension of the suspension and the quick sedimentation of the drug substance [32]. It has been deducted from this recent study that oral syringes should be provided instead of spoons or cups, as low doses can be better determined. Oral syringes without protective plastic caps are preferred as the cap cannot be ingested or aspirated accidentally [33]. Conventional teaspoons are not recommended because of their different morphology and the resulting varying dose volume.

2.5 Drug administration

Drug administration is another key factor in the treatment of children and elderly.

Often, the caregivers or patients must change the galenic principle of the drug formulation to enable the administration.The use of intravenous syringes for oral drug administration may be risky when the dose is accidentally given parenterally. Breaking ampoules for parenteral use and administering their liquid content perorally can only be applied if the stability of the drug substance in the gastrointestinal tract and the peroral bioavailability is well known. Macroscopic solid drugs have to be coadministered with a sufficient amount of liquid (at least 150 ml for an adult in an upright position) to prevent pill-induced oesophageal injury [34]. The required liquid volumes may sometimes be too large for neonates and infants. Drug administration in combination with food is sometimes problematic (e.g., mercaptopurine is completely degraded within minutes by xanthinoxidase which is still active in milk or milk products [30]). New application devices may facilitate drug administration to children (see Figure 2).

Drug formulations for administration into the buccal cavity are novel attractive dosage forms for use in paediatrics and geriatrics, as they combine the major advantages of solid drug formulations, namely high drug stability and non toxic excipients, with ease of administration. After placing buccal wafers or lyophilisates onto the tongue, these immediately dissolve and release the drug substance. A limitation of this principle is the taste of the drug substance.

2.6 Socio-cultural acceptability

Recently, some new developments have entered the market enabling drug administration without stigmatisation of the patient. Hence, a better compliance is expected. Examples are insulin application devices known as 'pens', transdermal patches or novel methylphenidate formulations. In order to prevent school-going children from stigmatisation, various capsule formulations with mixtures of different coated and uncoated pellets have been developed. The capsules are administered at breakfast time, and a second dose while the child is at school is no longer required because the drug is released by a second pulse, which imitates a school-time dose.

2.7 Product information

The product information provided with the drugs is still often unreadable for the patients or caregivers, causing numerous problems. For example, dry syrups are often prepared by the patients themselves or by the caregivers, but a number of errors can occur [32]. Therefore, it is recommended to prepare the ready-for-use suspension or solution in the pharmacy shop. Another problem is the labeling of the required doses at each age and condition. The labeling may significantly differ within a set of generic drugs of the same compound. An internationally standardised labeling concept is urgently needed.

Figure 3. Medication box of a geriatric patient.
Medication errors are probable.

3. Special formulations for the paediatric population

Very new dosage forms and application devices for paediatric use have been recently introduced into the market [10].

The dose sipping technology consists of a straw with film-coated micropellets which are ingested in combination with a liquid of choice (Figure 2). Any fluid that does not contain particulates can be used. Orange juice cannot be used as the fibers would block the porous controller. The micropellets may contain clarithromycine, which is an extremely bitter drug substance. With the dose sipping technology, the compliance significantly increases because of the neutral taste of the drug formulations during the ingestion and the free choice of beverage.

Another interesting application device is a pacifier that may be filled with nystatin for the treatment of oral soor. The neonate or infant can use it for hours, releasing approximately constant drug amounts and the parents can optically control the remaining suspension.

New dosing devices like the minipellet counter or dosing pen [10] have been developed to reduce the common dose for adults to be suitable for almost all children. However, it is still unclear whether they can be realised for drug products due to their high prices.

4. Special formulations for the geriatric population

The risk of drug administration errors is high in many geriatric patients. Some of these patients use medication boxes where various drugs are no longer labelled, and can therefore be easily mixed up (Figure 3). The stability of the drug and the dosage forms inside the medication box is unclear. Obliviousness of the drug intake is another issue. Multi-drug blister packages and electronic reminders may help in such cases.

Figure 4. Insulin pen InnoLet™ (Novo Nordisk) with improved visualisation of graduations for patients with reduced visual abilities.

The reduced visual abilities of geriatric patients may also limit the safety of drug use. In a few products, the graduations have been enlarged to improve the visability (Figure 4). The insulin pen InnoLet™ (Novo Nordisk) offers large graduations and can be activated by relatively low forces. In other pen types, up to 40 N are required to start the system. Some geriatric patients cannot achieve these forces with their fingers. De-blistering machines are available to facilitate the use of tablets and capsules from blister packages (Figure 5). A recently introduced eye-drop solution can be easily administered by the special medical device Xal-Ease™ (latanoprost ophthalmic solution by Pfizer). The required forces for dropping the solution are not reduced but the system is easier to handle for a patient with motor dysfunctions, compared with the conventional devices. The optical and tactile identification of drugs and medication packages still have room for improvement. Coloured solid dosage forms are a contribution to drug safety [35]. The Braille script has already been placed on most packages [36]. These are important steps for drug safety in geriatric patients, as most of them suffer from reduced visual abilities.

5. Expert opinion

The recently approved legislation in the European Community that will come into act in 2007, will be a big opportunity to improve the present situation with paediatric drugs, by forcing and funding the pharmaceutical industry

Figure 5. Eye-drop application device Xal-Ease™ (Pfizer) and deblistering machine for solid dosage forms in blister packs

to develop new formulations or dosage forms, and consequently to conduct clinical trials with the new paediatric drugs. A number of new concepts and ideas for better drug formulations, that are more appropriate for the paediatric subpopulation are available. Examples are the dose sipping technology and improved drug delivery devices. The authors expect an increase in the development of paediatric formulations, for new drug substances as well as for old compounds without exclusivity protections. From the first analysis of Shirkey in 1968 ('children are therapeutic orphans' [13]), it took about 40 years to react to the situation in paediatrics. However, there is still no similar programme for the geriatric population. It is hoped that it will not take another 40 years to include the requirements of the elderly into drug development. Formulation developers should keep in mind, in every project, that the problems in the geriatric population regarding drug delivery and drug application are quite similar to the paediatric situation. Potentially, geriatric patients can also profit from the expected new products for children. Providing the drug substance for every patient in a manner and formulation that is most appropriate will be a major and exciting challenge for the future.

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