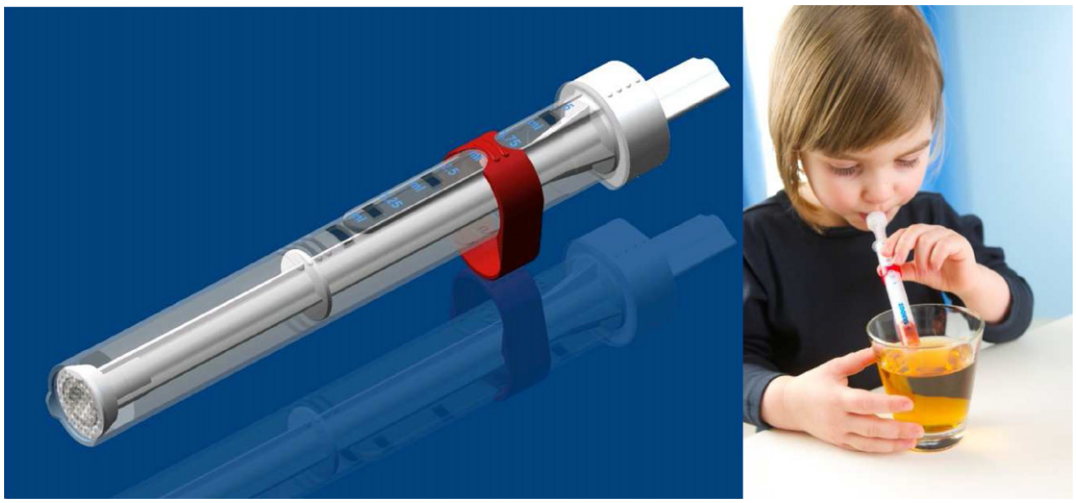

Fig. 4. Dose sipping syringe design (left) and child taking its medicine with the dose sipping syringe (right).

Having adjusted the prescribed dose with the surrounding plastic ring, the syringe is then filled by placing it into the liquid pharmaceutical and pulling the piston (Fig. 3). Alternatively, an adapter may be used which fits both to the syringe and the medicine bottle (Jakob et al., 2011). Then the pre-filled syringe is placed into a glass of liquid and the child may sip its favourable drink through the sipping device (Fig. 4). Doing so, a laminar flow assures complete uptake of the pharmaceutical while an unpleasant taste is suppressed by the floating drink.

Besides the safe and easy handling the dose sipping syringe assures dosing accuracy. Furthermore, the patient may decide which drink to have with the medicine. This freedom combined with the sophisticated yet simple drinking straw method distinctly contributes to a high compliance adherence. Additionally, the dose sipping syringe is designed to be re-used several times and hence is suitable for cleaning in the dishwasher.

Without any doubt, the awareness of the special requirements of paediatric drug delivery will significantly increase in the near future. RAUMEDIC already contributed to this emerging trend by the development of the above described devices. Of course, these devices are also beneficial for geriatric drug delivery since elderly patients often struggle similar issues than children (e.g., swallowing difficulties, non-compliance). Due to these reasons, RAUMEDIC is currently working on the development of further innovative drug delivery devices of the next generation.

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FDA: Contribution to developing pediatric formulations and transatlantic collaboration☆

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Pediatric drug products are pharmaceuticals intended for children ranging from birth till adolescence age. Since these products need to be administered to children across a broad age range. It is desirable that a platform technology would allow for easy titration to the desired dossier. Additionally a platform technology may entail a common formulation or novel drug delivery approach for a broad group of products with similar physicochemical properties, functional groups, and or pharmacokinetic properties. Such products must be easy to swallow and have acceptable organoleptic properties. The FDA-NIH intra agency collaboration was initiated with the aim of identifying drug products with pediatric needs, but lacking PhRMA interest for development, and to identify platform technologies based on the physico-chemical and pharmacokinetics properties of the drug substance. As an illustration of these platform technologies, a few drug substances will be selected for appropriate platform technology studies in the division of product quality laboratories.

Tablets are the most popular dosage forms among the general population as well as for the older, i.e., school age, children. For the children in the infants and toddler age groups liquid dosage forms such as drops, solution, suspension, etc. are preferred and may require an extemporaneous compounding from a tablet or capsule dosage form. In most cases, the solubility, stability and taste of

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the drug substance dictate the availability of a liquid dosage form. Drugs with high water solubility, i.e., biopharmaceutical classification system (BCS) class 1 and 3 compounds, may be formulated as oral solutions, while those with low water solubility, i.e., BCS class 2 and 4 compounds, require use of special techniques, such as salt formation, complexation, surfactants, cosolvents, etc., to formulate as oral liquid dosage forms. The recent World Health Organization draft document on the development of pediatric medicines also encourages use of flexible dosage forms, such as tablets that are easily dispersible in mouth or may be used to prepare oral liquid preparations suitable for young children (WHO, 2010).

Careful consideration should be given during the excipient selection for pediatric products especially those for neonates and very young children. The amount and number of excipients should ideally be kept at a minimum. The selected excipients should be generally regarded as safe (GRAS) substances with documented human use in the proposed levels and be listed in the FDA's Inactive Ingredient Guide. A comprehensive evaluation of the safety and toxicity of the selected excipients should also be conducted at the maximum daily administered dose to ensure absence of unwanted adverse events in the target population. Such studies ensure that excipients which are otherwise used safely in adult population do not end up causing unintended toxicity when administered to children in very large quantities, e.g., benzyl alcohol, propylene glycol, etc (Shehab et al., 2009). Several new molecular entities are BCS class 2 compounds and these compounds are especially challenging to a formulation scientist. To overcome these challenges the formulation scientists tend to use novel excipients or the existing excipients in amounts that may pose a danger to pediatric population.

Good palatability is essential to ensure acceptability by the patient. However, a number of drugs for common aliments have very bitter taste. Examples include anti-malarial drug chloroquine, antibacterial drugs amoxicillin and clindamycin, and immunosuppressant drugs prednisone and prednisolone, and many of the HIV/AIDS drugs. Some of these studies are ongoing in division of product quality laboratories. The bitter taste necessitates the use of appropriate techniques to ensure effective taste masking of the drug. These include:

(a) Use of natural and synthetic sweeteners and flavoring agents. This is the simplest and easiest approach for taste masking but may not work with very bitter drugs. Examples include fruit flavors (e.g., strawberry), essential oils (e.g., peppermint), herbs and spices (e.g., cinnamon), sweeteners (e.g., sucralose), etc.
(b) Use of a pro-drug molecule with reduced bitterness and low toxicity profile. The pro-drug is converted into the drug substance in the gastro-intestine tract. Examples include clindamycin palmitate hydrochloride, tenofovir disoproxil fumarate.
(c) Formation of less bitter salts or cocrystals, e.g., lamotrigine, cetrizine hydrochloride.
(d) Use of polymer coating to reducing oral solubility of drug. The pH of human saliva ranges between 5.5 and 7.5, while the pH of the stomach ranges between 1.2 and 3.5. Thus the bitter taste of a drug may be completely masked by using appropriate coating materials (e.g., polyacrylates) which are soluble in acidic pH but exhibit limited or no solubility in the salivary pH range. A fluidized bed assembly (Fig. 1a) may be used to coat the drug particles by directly spraying a layer of taste masking polymer on them (Fig. 1b). In case this approach is not feasible due to the physico-chemical properties of the drug a two step process may be used in which the a solution/dispersion of drug substance in a film forming polymer solution is sprayed onto an substrate, followed by coating with the taste masking polymer layer (Fig. 1c). The substrate used could be particles of an inert excipient, such as microcrystalline cellulose, or small size spherical beads of an inert excipient, e.g., sugar, cellulose, etc. The temperature and velocity of the inlet air and the spray rate of the coating solution must be carefully controlled to ensure optimum coating efficiency and to avoid aggregation of the drug particles/granules.
(e) Complexation of drug molecules with other chemicals to reduce the oral solubility of drug or to decrease the perception of bitter taste by reducing the interaction of the drug particles with the taste buds in the mouth. β-Cyclodextrin, an inert, nontoxic, oligosaccharide from starch, and tannic acid, a polyphenol tannin, are sometimes used as complexing agents. It is important to justify the inclusion of complexing agents or other excipients when there is a documentary evidence of toxicities. Other chemicals used may sometimes include water insoluble, high molecular weight cross-linked polymers containing salt forming groups e.g., amberlite. Complex formation causes the conversion of the crystalline drug into its amorphous state. Hence the formation and stability of the resulting complex may be monitored using differential scanning calorimeter (Fig. 2), X-ray powder diffraction pattern and solid state nuclear magnetic resonance studies.
(f) Formation of a solid solution or solid dispersion of drug substance in an inert carrier matrix (e.g., povidone) by mixing and melting the drug and carrier, followed by quick cooling or by dissolving the drug and the carrier in a common solvent followed by evaporation of the solvent.

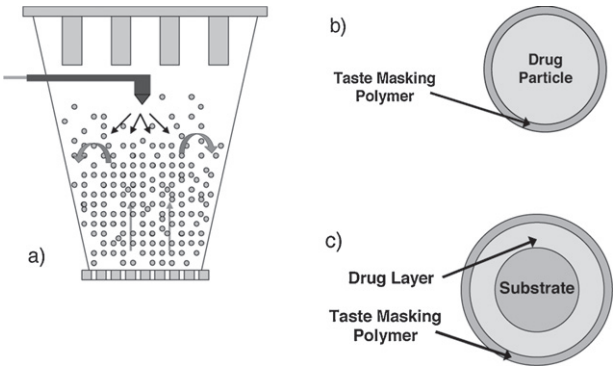

Fig. 1. (a) Fluidized bed spray coating; (b) taste making polymer coating of drug particle; (c) taste making polymer coating on drug layered substrate.

Thus, a number of formulation approaches exists which may be used to mask the taste of bitter tasting drugs. Once the taste is masked, other organoleptic properties may be modulated judiciously. The FDA-NIH intra-agency collaboration as well as interactions with EMA, WHO, are underway to identify scientific and technological gaps and understand dosage form platforms. All the findings will be published in national and international jour-

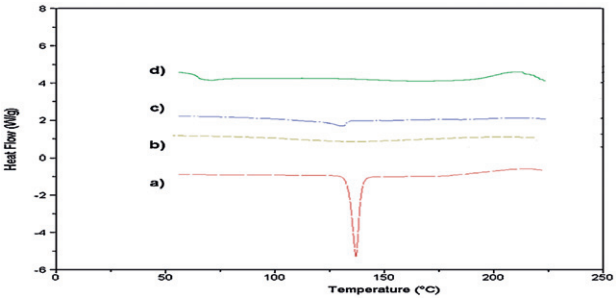

Fig. 2. DSC profiles of (a) drug; (b) complexing agent; (c) physical mixture of drug and complexing agent (1:7); (d) complex between drug and complexing agent (1:7).

nals and presented with transatlantic collaborations. The platforms may be used to develop products for all ages for a broad category of molecules for pediatric population.

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Off-patent Oral Oncology Drugs for Kids (O3K FP7-project): From bedside to PUMA

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There is an urgent need for appropriate oral formulations of anticancer drugs for the treatment of paediatric malignancies in children of all ages. The goal of the O3K consortium is to develop oral liquid formulations of cyclophosphamide and temozolomide, important chemotherapeutics which have been identified in the list of paediatric needs by European Medicines Agency (EMEA/197972/2007).

Both off-patent drugs are widely used orally for the treatment of childhood cancer. However, the currently available tablets (cyclophosphamide) and capsules (temozolomide) are not suitable for use in a paediatric setting, particularly in infants and young children, as it is often impractical for them to be swallowed. This is a major health concern since these children do not readily have direct and safe access to these curative drugs.

O3K will conduct the pharmaceutical, clinical and pharmacological studies required for the development of these oral liquid formulations. Upon completion of the project, a dossier containing data required for application for a Paediatric Use Marketing Authorisation (PUMA) will be filed for both products. O3K will provide access to curative drugs for all children with cancer, improving compliance, ensuring safety for both patient and environment and allowing the development of essential ambulatory treatments.

In accordance with ICH guidelines, the development of these agents will lead to improved quality and safety of paediatric drug formulations. The O3K project involves 9 partners (including 5 institutions and 3 SMEs providing significant expertise in clinical and pharmacological research relating to paediatric oncology along with 1 parents organisation) from three European member states (UK, Italy and France).

1. Introduction

Childhood cancers represent a rare disease accounting for less than 1% of the total number of cancer cases in humans. Across the whole of Europe, approximately 16 000 new cases of childhood cancer are diagnosed in children under the age of 19 each year. Despite the high cure rates now being achieved for certain tumour types (e.g. 80% five-year survival rates for Wilms tumour and acute lymphoblastic leukaemia), cancer remains the major cause of death from disease beyond the age of 1 year with approximately 3000 children dying from cancer each year in Europe.

During the last 30 years, access to innovative therapies developed by pharmaceutical companies has been extremely limited for children in Europe, one reason being that Paediatric Oncology does not represent a large, and hence financially attractive, area for drug marketing. In Oncology, new drugs are not usually studied at first in healthy volunteers, but in patients whose disease is refractory to all standard treatments. In children with cancer, new drugs are proposed when all the treatments known to be active in their disease have failed. Most of the anticancer drugs currently used in children have been developed by academic groups through prospective clinical trials using the drugs and formulations available for use in adults. This allowed the generation of clinical and pharmacological paediatric data for compounds that eventually went off-patent. However, there are still data missing for many off-patent oncology drugs, due to the lack of commitment by pharmaceutical companies. In particular, age-appropriate oral formulations of many important anticancer drugs have not been developed.

Oral chemotherapy is used on a daily basis to treat paediatric malignancies. Some drugs are indicated for oral use only. For example, oral temozolomide has gained popularity for the treatment of refractory brain tumours in children; 6-mercaptopurine is a major component of maintenance chemotherapy for acute lymphoblastic leukaemia. In addition, health care providers have to deal with the tablets or capsules that are available. For example, when a compound is to be given daily, the entire dose for one week is given on 4 or 5 days. In other situations, intravenous formulation may be given in the form of a drinkable solution. However, this may increase the risk of serious adverse reactions or inappropriate dosing due to poor or inconsistent bioavailability. Oral administration of anticancer drugs is a major concern in children under the age of three years. This is particularly important as paediatric malignancies in children under the age of three represent 30% of all paediatric cancers.

The O3K project will develop and evaluate new galenic formulations of two already available anticancer drug widely used in paediatric oncology with a well established safety and efficacy profile. Indeed, products, i.e. cyclophosphamide and temozolomide, have been widely used in adults and in several paediatric malignancies, with adapted posology, for many years. However, commercially available tablets and capsules are not suitable for use in all children, in particular those who cannot swallow, and among them children below the age of three. Children are not small adults. They differ from adults in development, physiology, psychology and behaviour.

There is clearly an urgent need for appropriate oral formulations that permit accurate dosing, enhance patient and compliance and improve access to safe and efficacious anticancer medicines for children, particularly in infants and very young children. There is a need to generate appropriate PK data in the entire paediatric population for cyclophosphamide, in particular when those data are not available to support current doses and schedules for children.

2. Concept and objectives

The new EU regulation on medicinal products for paediatric use (EC1901/2006) came into force on January 26th, 2007. This regulation aims to improve the health of children in Europe by:

- Stimulating research and development of medicines for use in children
- Ensuring that medicines used to treat children are appropriately tested and authorised