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Time to change the paradigm of children's medicines from liquid formulations to flexible solid oral dosage forms

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Worldwide, people prefer a liquid formulation when paediatric medicines have to be given orally. The syrups and suspensions can be dosed flexibly by increasing the volume with age and weight of the child. We believe that young children can swallow liquids better than solids and prefer to take a sweet tasting liquid medicine. Simply liquid medicines are what children choose if they are given the chance – or at least that is what we adults think. When new innovative medicines are developed for use in children, the global pharmaceutical industry usually develops a liquid formulation for children if the medicine is to be given orally. In rich countries liquid formulations for oral medicines continue to be the rule.

In resource limited settings (RLS) age appropriate paediatric formulations for children are not commonly available [1, 2]. If what the pharmaceutical industry develops for children are liquid formulations, then one could think that the lack of paediatric medicines in RLS could be just a consequence of the general lack of availability of children's medicines in those settings. But what if the domination of liquid oral formulations as the perceived first choice for children is in fact also a cause and not only a consequence of the problem of poor availability of age appropriate paediatric medicines in RLS? Indeed, liquid oral formulations possess problematic characteristics particularly relevant in RLS [1]. Logistics of liquid oral formulations are complicated by increased bulk and commonly need cold-chain, problems for both the professional of bulk transport, and for the family who has to carry the child's medicines home. From a pharmaceutical development and manufacturing point of view, liquid medicines are problematic in many ways. Taste-masking is challenging, liquid formulations require more excipients than solid ones, and some excipients may not be suitable for children. Importantly, liquid formulations are more expensive to produce than solid dosage forms. The higher costs of production and logistics make liquid medicines more expensive than medicines in solid formulations. A switch to solid oral paediatric formulations would be a way to improve availability of paediatric medicines, if only the children would accept them and be able to swallow them.

May be we should ask the children! That is exactly what we did in Helsinki in 1999 when we interviewed 150 children who were 3-7 years old and

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their parents at a health centre emergency department [3]. The great majority of the parents preferred to give a liquid formulation for their children who were 3-5 years old. A small majority of parents preferred a tablet for children who were 6-7 years old. The 103 children who had experience of taking the index formulation were interviewed. All of them had taken a liquid formulation, 75% had taken tablets or capsules, 49% lozenges and 29% chewable tablets, mostly vitamins and fluorides, the last usually as 4 mm mini-tablets. For 47% of children, tablet was their preferred choice, for 44% a liquid and only 9% of children preferred suppositories. Tablet was the preferred choice in nearly half of the children even in the youngest age group of 3 years. Could it be that the children were just dreaming of taking tablets, because they remembered the bad tasting liquid medicines they had been given?

Several studies have since investigated the opinion of children about oral formulations, and also studied in an experimental setting how the young children are able to take different formulations, particularly the new mini-tablets (diameter 2-5 mm) [4-7]. In a randomised cross-over study of 306 children aged 6 months to 6 years the children accepted a 2 mm placebo mini-tablet significantly better than a sweet syrup (placebo) and were also able to swallow the mini-tablets more reliably than the syrup, including those in the age group of 6 months to 1 year [5]. A similar study of 152 neonates age 2-28 days showed that they accepted the mini-tablets as well as the syrup. The swallowability of mini-tablets was not inferior, may be even higher compared with syrup. No serious adverse events occurred and particularly none of the neonates inhaled or coughed out either of the formulations [4]. In another randomised cross-over study 183 children aged 1-4 years were administered four oral placebo dosage forms that were aimed at neutral taste, at home, on four consecutive days once daily, except twice on one day only. The formulations included 4 mm mini-tablets, powder, suspension and syrup. The acceptability was significantly higher for the mini-tablet than for the suspension. The estimate of the mean number of intakes fully swallowed was also significantly higher for the tablet than for the other formulations. Both children and parents preferred the mini-tablets and syrups to the suspensions and powders [7].

Mini-tablets are one form of flexible solid oral dosage forms. Other examples include granules (pellets), tablets that are oro-dispersible or that can be used for preparation of oral liquids. Some of these can be used for oral medicines requiring precise dose measurement or titration, particularly the multiparticulate solid ones (granules dosed with a measuring device, and those that could be dispersed to form a liquid dose). Also, small mini-tablets of appropriate strength could be relatively flexibly dosed by giving more than one mini-tablet, as even newborns accept and are able to swallow them. However, not all medicines require precise dose measurement or titration, although doctors prescribing, pharmacists dispensing and nurses administering the medicines are taught and trained as if all medicines would need that. As an example, for most of the common antimicrobials, such as penicillins and cephalosporins, what is really important is that the given dose is adequate. Underdosing, in addition to being ineffective, could increase emergence of antimicrobial resistance. Dose related toxicity of these medicines is either not known or unlikely with oral dosing. Some other medicines have a narrow therapeutic index and need exact dosing, necessitating higher demands on the dosing flexibility of the formulation. The formulations based on solid platform technology can, in contrast to liquid formulations, be manufactured also in slow-release form, which allows less frequent dosing as for example with valproate modified-release granules [8].

The WHO Informal Expert Meeting on Dosage Forms of Medicines for Children, held in Geneva, Switzerland in December 2008 came to the conclusion that the dosage forms of medicines most 'suitable' particularly for developing countries are flexible solid dosage forms. These dosage forms could be used for many of the medicines that are necessary to treat the common diseases in children under 5 years old such as lower respiratory tract infection, malaria, diarrhoeal diseases [9]. Since then such formulations have become increasingly available for children with diseases like malaria and HIV [10,11]. The big donors have started to follow the advice given by the WHO, and paediatric flexible solid oral dosage forms seem to be appearing more rapidly in RLS settings than in rich countries. Hopefully flexible solid oral dosage forms soon will become the first choice when new paediatric medicines are developed in the US and EU who have in place initiatives in the form of incentives, rewards and legal requirements for development and study of all new medicines that could be of therapeutic benefit to children [12]. Substituting oral liquid formulations with suitable solid dosage forms would bring considerable cost savings even in rich countries [13]. It is time we adults start to listen to the children and accept that flexible solid oral dosage forms are the new paradigm of first choice for developing, procuring, prescribing and demanding medicines for children.

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