



Paediatric Dosage Forms: A Review of Age Development and Dosage Forms of Choice

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ABSTRACT

Paediatric medication development has advanced extensively worldwide due to legislative encouragements and requirements directed towards the development of studies of drugs for use in the paediatric population (FDA, 1994). European Medicines Agency (EMA) has reviewed its legislative requirements to drive innovations in paediatric formulations (European Commission, 2013). An approved paediatric investigation plan is required for all new drugs and all line extensions that are submitted for EMA approval after January 2009. Such plans should cover all paediatric age groups. Furthermore, the EMA has issued guidelines on pharmaceutical development of medicines for paediatric use including route of administration, dosing frequency, excipients, patient acceptability, container closure systems and devices and user information (CHMP, 2006, Gauthier and Cardot, 2011). The FDA has issued in 2012, a law requiring the implementation of the Paediatric Research Equity Act and Best Pharmaceuticals for Children Act (Christensen, 2012). Similar to the EMA requirements, a paediatric study plan (PSP) is required for submission and approval by the FDA (FDA, 2013). Oral route of administration is inevitably the most popular route of delivery due to ease of ingestion, availability of a wide variety of dosage forms and most significantly enhanced compliance and adherence. Different drug formulations can be administered orally, including solid and liquid dosage forms (Fasano, 1998, Sastry et al.,).

Keywords: Paediatric dosage, Drugs, Children act.

INTRODUCTION

The provision of safe, as well as effective, pharmacotherapy in paediatric necessitates the availability of medicines alongside information for proper utilization, which is compliant with the patient's age, physiology and body surface area (Mulberg et al.,). Therefore, dosage forms formulated specifically for children, are often required. Till date, the utilization of unlicensed (medicine with no marketing authorisation) as well as off-label medicines in paediatric is extensive (Mason et al.,). The

disadvantages of this being that there are limited studies on their effects on the paediatric population; age-appropriate formulations are usually not presented, and available formulations are not licensed for paediatric use (Choonara and Conroy, 2002) [1-5]. The paediatric population is heterogeneous; ranging from new-born to young people, with large physical as well developmental differences, regarding pharmacokinetics and pharmacodynamics. Organ development, metabolic competence and skin maturation are some factors that may vary based on

age, particularly in early infancy. The paediatric age groups

recognized by ICH are shown in Table 1 (EMA, 2006).

Table 1: Classification of paediatric based on age groups

• Preterm new born infants
• Term new born infants (0–28 days)
• Infants and toddlers (28 days–23 months)
• Children (2–11 years)
• Adolescents (12 to 16 or 18 years (dependent on region))

Paediatric dosage forms

Paediatric dosage forms should be versatile so that drugs can be administered to neonates, children, and adolescents. The common paediatric dosage forms include solid dosage forms (such as tablets); powders, solutions, and syrups (Viner and Barker, 2005). Solid dosage forms are drugs, which have been compounded to give a definite shape and a standard dose, as is the case with tablets. Powders are a type of solid dosage form, which have been ground and are finely divided. They are usually administered topically on the skin, sprinkled on food or mixed with liquid diet. On the other hand, solutions are dosage forms which are made up of an aqueous base (majority) and other pharmaceutical ingredients which give the solution its therapeutic effect. Syrups form sugary and have a thicker consistency than solutions, a factor which makes them more viscous (Ansel et al.,) [6-10].

Age development and dosage forms of choice

Dealing with children is quite challenging, particularly when it comes to diseases and their remedies. For neonates, the challenge is even more pronounced because diagnosis alone poses a difficult step. After diagnosis, other challenges include the appropriate choice of formulation and route of administration. Children are remarkably sensitive to the effects of drugs; not just on the internal effects that the drugs have but also on the outward appearance and the taste. A

child may refuse to take a drug because the colour is not appealing or because it smells 'weird'. Even after succeeding in making the child swallow the drug in the first instance, this result may not be repeated for subsequent doses. This is because children have a unique fine memory to conditions, circumstances, and experiences of their past (Sahler et al.,). To say the least, it will pose a massive challenge trying to convince them to take the drug again. For this reason, paediatric dosage forms need to be tailored to address the fears and the expectations of the target users. This request for a higher level of interest during manufacturing and even prescribing, since children require lower dose amounts to achieve the same effects as seen in adults. In addition, various factors need to be taken into consideration, notably taste masking. For drugs that come in the form of powders, the dosage form can be changed by tableting the powders and converting them into solid dosage forms. Powders can also be granulated to make it easier to determine the dose since this becomes a major issue, especially with regard to children (van Riet-Nales et al.,).

Table 2 shows a matrix developed by the EMA from responses to questionnaires sent out to 40 participants (including parents, pharmaceutical scientists and clinical pediatricians) in different European countries to develop a relationship between age development, dosage form and route of administration (Cram et al.,). Moving from the left to the right, the emphasis in the columns changes from the applicability to preference.

Table 2: EMA matrix relating oral dosage forms/ route of administration to dosage form and age; adapted from references (EMA, 2006, Breitzkreutz and Boos, 2007)

Oral dosage forms	Preterm new-born infants	Term new-born infants (0 d-28 d)	Infants and Toddlers (1 m-2 y)	Children (pre-school) (2-5 y)	Children (school) (6-11 y)	Adolescents (12-16/18 y)
Solutions/ drops	2	4	5	5	4	4
Emulsion/Suspension	2	3	4	5	4	4
Effervescent dosage form	2	4	5	5	4	4
Powders/Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersible dosage form	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Key

Younger ages (preterm-pre-school): 1- not applicable, 2 - applicable with problems, 3 - probably applicable but not preferred, 4 - good applicability, 5 - best and preferred applicability.

Older ages (school-adolescents): 1 -not accepted, 2 - accepted under reserve, 3 -acceptable, 4 -preferred acceptability, 5 - dosage form of choice.

Definition of acceptability

The acceptability of a drug is its ability to meet the patient's requirements and needs. Acceptability also entails the quality of the drug to realize the objectives set out by the physician. It involves a number of aspects including the dosage amount and proper diagnosis. Of the two, proper diagnosis is of immense importance before embarking on managing an ailment, a condition, or a disorder. Proper diagnosis not only gives the physician the knowledge of the condition in question, but also provides a head start on the best way of managing it. Managing in this case, refers to administration of the right medicine. As mentioned earlier, the administration is determined by a number of factors. This calls for a choice on the route of administration to be used. The route of administration should be in line with the pharmacokinetic properties of the drug. For example, drugs

that are absorbed in the stomach are administered orally. Care has to be taken regarding some drugs taken orally, as they may undergo breakdown while in the stomach. Such drugs (proton pump inhibitors, omeprazole) are usually enteric-coated to minimize, if not effectively curb, their breakdown as they pass through the gastrointestinal tract (Standing and Tuleu, 2005). Enteric coating provides a layer that inhibits the action of acids enzymes present in gastric juice and other stomach secretions, which contribute to the breakdown of the acid sensitive's active pharmaceutical ingredients (APIs) in the formulation. If such drugs are not enteric-coated, there is a high likelihood that they will undergo breakdown while still in the stomach, and the APIs may fail to reach their intended area of absorption, which could be the ileum or even the large intestine (van Riet-Nales *et al.*, 2013).

Important factors in the overall acceptability of an oral paediatric medicine

For oral paediatric medicines to be acceptable and therefore effective there are a number of factors that need to be considered. One of these is elegance. Elegance refers to the outward appearance of the dosage form and its ability to appeal to the eye. Among children, this factor becomes crucial because of the sensitivity of children to seemingly unimportant matters (EMA, 2006) [11-15]. A child may refuse to take a medicine just

because it does not look appealing. A factor related to acceptability and which is closely related to elegance, is palatability. Children will rarely take drugs that are bitter tasting (Hoppu, 2008). For this reason, most drugs which have a bitter taste are coated with a sweet tasting substance. If the bad taste is not masked, such drugs may predispose the child to vomiting. If the smell of the drug is putrid, it may also negatively influence the acceptability of the drug. The ability of children to differentiate drugs by their smell is testimony of their attention to detail. In the same way, a dosage form needs to be convenient for it to be acceptable among children. The term convenience refers to the method by which it is administered, for instance, as a tablet, syrup or as a powder. Among children of school age, tablets are more popular compared to powders because they can easily be administered (Nunn and Williams, 2005). Dosage is also accurate and can be easily determined since most tablets are already portioned in specific doses. Syrups are also more popular compared to solutions, which in turn are preferred over powders (Maheshwari et al.). Excipients added in solutions to increase their volume should be neutral and need not have an effect on the ultimate intended therapeutic effect of the drug. Lastly, the stability of a drug is of great importance with regard to its acceptability. Stability is the ability of a drug to maintain its original form in terms of physical appearance, its therapeutic effects, and its chemical composition (Allen and Ansel, 2013). A medicine whose chemical structure varies after a period, or changes taste, is likely to have low acceptability compared to the one whose properties do not vary. In addition, the drug may not produce the intended outcome, especially if both chemical and therapeutic variations occur (Overgaard et al.) [16-20].

A WHO consultation on paediatrics and guidelines

The World Health Organization (WHO) is the international body that controls products and services with regard to human health. As such, it has laid down guidelines and procedures for production of paediatric dosage forms. WHO recognizes the need to develop drugs and formulations that specifically target children. It admits that even though the search for the appropriate dosage formulation with regard to the age, physical and physiological conditions of children has

been challenging, it is not a lost war (Hill, 2011). However, WHO warns against administering unlicensed drugs to the paediatric population, as this is likely to culminate in grave consequences. WHO recommends that dosage formulations should be prepared to cover as wide an age bracket as possible. This is because the age bracket of children is vaguely defined and stretches from preterm infants to term infants, to toddlers and even adolescents. It also recommends that manufacturers uphold good manufacturing practices with regard to obtaining and processing raw materials, up to preparation of the final pharmaceutical product. WHO stipulates that the dosage administered should be in line with the age and specific needs of the child. More importantly, the dosage, whether in volume or size, needs to be accurate. An overdose or an under dose may result in toxicity or sub therapeutic effect respectively. In addition, paediatric formulations should be made in ready-to-use preparations, as much as possible. This will minimize, if not eradicate, the need to modify the preparation by parents or health care professionals.

According to WHO, the dosage form should be acceptable and palatable. Furthermore, the drug formulation should be palatable without the need to mask the taste or sugar coating. Palatability will make it easier for children to accept and swallow the drug. Acceptability of the dosage formulation stretches beyond its use among children and extends to parents/caregivers and physicians – the dosage formulation should be acceptable among parents to increase its chances of being purchased. At the same time, acceptability or palatability should not be enhanced by mixing the drug formulation with food or drinks. This is because food and drink may affect the absorption of the drug or may interact with it, resulting in physical or chemical alterations. If there is no alternative, then the food or drink should be in a small amount such that it will not have an impact on the effects of the drug (Kozarewicz, 2014). Manufacturers also need to indicate whether it is possible to administer a given drug with food or beverages, and also incorporate any exceptions. When administering drugs to children, it should be ensured that minimum dosing is adhered to. The frequency with which a drug is administered should be made minimal because frequent dosing, especially more than twice a day, may have a negative impact on patient compliance (Greenberg, 1983) [21-26].

WHO recommends that manufacturers should aim at production of quality dosage formulations, with the needs of the target population in mind. For instance, the dosage formulation should be affordable to most people and the production process should be simple. The drug should be able to reach the target population easily by implementing viable transport and supply strategies. In addition, instructions for proper storage of the drug should be made available. For drugs that need to be dissolved in water before being swallowed or those that need water when swallowing, procedures for obtaining standard clean water should be outlined. This is because clean water may not be locally available in some locations (Hill, 2011) [27-29]. Furthermore, the need to produce dosage formulations that are effective among the paediatric population has brought up the need to conduct further research in the field of excipient's toxicity. As a result, newer methods, which are still under trial, are being investigated to study the effect of commonly used excipients in dosage form development, and their impact on the paediatric patient population (Walsh and Mills, 2013).

The excipients used in making paediatric formulations have witnessed an increasing interest, with the belief that the right excipient will be the answer to most of the questions that still remain unanswered.

To begin with, the excipients to be employed need to have a high safety profile to prevent any side effects. They also have to be tolerable because this influences the acceptability of the paediatric formulation. Current research projects of excipients used in paediatric formulations incorporate all stakeholders, including the target age group (children), medical practitioners, and even parents/ care-givers (Fabiano et al.,).

Standard features of dosage forms for paediatrics

The goal is to find one formulation suitable for every age group. The primary focus should be the safety of the formulation and ideally cover as broad an age range as achievable. The guiding standards for choosing paediatric dosage forms should be based on the risk/benefit ratio accounting for the precise needs of this susceptible population. Desirable characteristics of quality paediatric drugs common to different kinds of dosage forms are outlined in (Table 3) [30-36].

Table 3: Standard features for dosage forms of paediatrics are outlined by WHO (2010)

Convenient, reliable administration	The administered dose should contain an amount of API adjusted to the age and needs of paediatrics. More than one dosage form of API or strength of a dosage form is required to cover different age groups. The intended dose volume or size should be appropriate. Paediatric medicines should be ready to administer. Manipulation of dose should be minimal.
Acceptability and palatability	Acceptability is the overall acceptance of the dosage form regardless of the route of administration. Acceptability depends on suitability for the particular age group, dosing device for a liquid medicine, palatability of an oral medicine, dose volume or size to be administered, appropriate packaging, clear and accurate labelling information and directions for use. Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size and texture of a medicine to be administered in the mouth. Compliance can be highly dependent on palatability. API palatability may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should, however, not become too attractive to the child (e.g. a sugar-coated tablet that is candy-like) in order not to increase risk of accidental poisoning.
Minimum dosing frequency	Minimal dosing frequency should be attempted. Instructions on the dosing frequency are based on the pharmacokinetic as well as pharmacodynamics properties of the API, but may also be influenced by the design of the dosage form. Frequent dosing may conflict with the lifestyle of older children.
End-user needs	It is important that dosage forms are convenient to produce, as well as

affordable. It is also important to bear in mind supply chain considerations such as ease of transportation and storage requirements. Storage in a refrigerator by the user is not always possible. Depending on age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, in developing the product, minimum dose volume and size should be attempted. Lack of access to clean water is an important issue to take into consideration in the development of medicines to be dissolved, diluted or dispersed prior to administration, as it may compromise the quality. It may be necessary to educate patients on how to obtain water of suitable quality, e.g. boiling or filtering instructions. Provision of the liquid vehicle as a part of the package may be an option to be considered, or the dose may be dispersed or dissolved in suitable food or beverage prior to administration. Instructions on such use should always be labelled.

Dosage form development for the paediatric population should ensure global application including addressing limitations such as lack of appropriate storage conditions,

cost of production and the lack of access to clean water encountered in developing countries. A flexible dosage form platform should also be used to ensure delivery of a wide range of APIs.

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