Available online on 15.07.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Formulation Design and Pharmaceutical Considerations for Paediatric Patients: Current Status and Future Dimensions

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ABSTRACT

Present day's conventional pediatrics doses forms are not very attractive towards the children. Due to various reasons such as larger size, bitter taste etc. pediatrics patients rejects the present conventional doses form in many cases. So, there is need for development of some attractive and effective dosage form for children. Present day's conventional pediatrics doses forms are not very attractive towards the children. Due to various reasons such as larger size, bitter taste etc. pediatrics patients rejects the present conventional doses form in many cases. So there is need for the development of some unconventional dosage forms that proves to be attractive towards the paediatrics populations. This review provides possible advantages and disadvantages of the present conventional dosage forms available for children. Hence present review introduces to various alternatives and unconventional dosage forms *viz.* effervescent granules / tablets, oral disintegrating tablets and medicated candies and their advantages and disadvantages.

Keywords: Effervescent granules, effervescent tab, medicated candy, Oral disintegrating tablet and pediatrics.

Article Info: Received 21 May 2019; Review Completed 24 June 2019; Accepted 30 June 2019; Available online 15 July 2019

Cite this article as:

Naman S, Madhavi N, Singh M, Singh PA, Bajwa N, Baldi A, Formulation Design and Pharmaceutical Considerations for Paediatric Patients: Current Status and Future Dimensions, Journal of Drug Delivery and Therapeutics. 2019; 9(4):601-606 **http://dx.doi.org/10.22270/jddt.v9i4.3031**

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INTRODUCTION:

Pediatrics patients differ from adult in various aspects of pharmacotherapy, including the abilities of drug admistration, medicine related toxicity and taste partialities. It is very much important that pediatrics drugs should best fit the child's size, age and various physiologic conditions of the children. To confirm suitable treatment for all pediatrics patients, various routes of administration, dosage forms, and strengths may be required. Selecting and designing a suitable dosage form for the pediatric patients is challenging. In addition to those problems usually faced while developing adult dosage forms; developing a dosage form for children poses other challenges such as the diversity of the patient population both in terms of size and physiological conditions[1]. Many present formulations such as tablets, capsules, suspensions, syrups for pediatrics are not suitable, they often leads to various types of problems in pediatrics such as chocking due to larger size of dosage form, vomit out due to of bitter taste of various oral dosage forms, difference in dosing in liquid dosage forms, unbearable pain in case of injection, ethical issue arises due to rectal forms. This review highlights current knowledge on various dosage forms for infants and preschool children. The pros and cons of the various types of pediatric dosage forms are summarized in this review[2].

Table 1: Various childhood stages according to age of children[3]

Stages of childhood	Age
Preterm infants	New born
Term new born infants	0-27 days
Infants and toddlers	1-23 months
Children	2-11 years
Adolescent	12-18 years

Various dosage forms available for pediatrics populations are

i) Oral route:-

***a)* Tablets**

Tablets are solid dosage forms usually prepared with the help of appropriate excipients in Fig. 1(a). A tablet varies in many features such as shape, size, hardness, thickness,

disintegration and dissolution property depending on the proposed use and method of preparation of tablets. Tablets are generally administered orally. Most of tablets consists of colorants and consisting of various type of coating. Tablets are generally prepared by compression of granules or powdered material under high pressure and very less number of tablets are prepared by molding. Some tablets have grooved which allows them to break down easily in two parts[4]. Tablets are commonly used for the treatment of diseases in pediatrics populations above the age of 2 years Tablet are one of the stable dosage forms that are easy to administer and easy to use. But due to size consideration and bitterness of tablet, these are not very compatible towards the pediatric population.

b) Capsules

Capsules are solid dosage forms in which medicinal product or inert substances are inserted in shell of hard or soft gelatin capsules shown in fig. 1(b). Gelatin capsules shells may be of hard or soft depending on their constituents. The shells of capsules are divided into a body and a cap. However it is common in hospitals for a caregiver to give open capsules or crush tablets to mix with food or drink especially for children or other patients unable to swallow solid dosage forms. Most of commercially available tablets are made up of hard gelatin capsules. Soft gelatin capsules made up of glycerin or polyhydric alcohol are generally used for encapsulating liquid materials, pasty materials and even tablets of smaller size[5]. Capsules are generally given to children more than the age of 2 years. Constituent of capsules can be mixed with food material according to advice of doctor.

c) Solutions

Solutions are liquid dosage forms consists of two or more substance dissolved in a suitable solvent or a mixture of mutually miscible solvents. It can be classified as oral, tropical, or ophthalmic based on the pharmaceutical application. It may also be classified on the basis of the constituents such as syrup (aqueous solution containing sugar), Spirit (solution containing mixture of aromatic compound and water), sweetened hydro alcoholic (solution consisting of mixture of water and ethanol). Solutions are one of the dosage forms that are very compatible too any age group of pediatric population[6,7].

d) Suspensions

Suspensions are defined as dosage forms containing divided drug molecules uniformly in a vehicle in which drug molecules exhibits lowest solubility. Usually suspension consists of powdered drug molecules suspended in suitable vehicle mostly purified water. There are various reasons of preparation of Suspensions over suspensions such as some of drugs are quite unstable in solutions but they are quite stable when suspended. In pediatric patients liquid form is preferred over solid form of drug due to ease of swallowing. The disadvantage of particular dosage form is disagreeable taste of un dissolved drug molecules[6].

ii) Parenteral

Parenteral refer to injectable route of drug admistration. Drugs can be injected into any parts of body i.e. joints fluid area (intra synovial area), spinal column (intra-spinal), arteries (intra-arterial), and, in heart (intra-cardiac). Parenteral routes are generally employed in the case of emergency where there is urgency of drug delivery is required or in the case where patients is not able to accept the drug or unable to tolerate the oral route of medication[7,8].

iii) Transdermal route:-

Transdermal route refers to delivery of drug through skin in general circulation of body. These are the easiest and painless mode of admistration of drug but have some side effects such as local irritation or unintended toxicity in the body. Ointments, Creams and gels are various semisolid dosage forms intended for topical delivery of drug[8].

a) Ointments

Ointments are semisolid dosage forms intended for external application on skin or mucous membranes[8]. Ointments may or may not contain medicament. Non-medicated ointments are generally used as lubricants, emollients or protectants.

b) Creams

Creams are semisolid dosage forms consisting one or more medicinal compound dispersed in either in oil in water (O/W) emulsions or water in oil (W/O) emulsions. Creams are generally preferred over ointments because creams are easier to spread and remove[9].

c) Gels

Gels are semisolid dosage forms consisting of dispersions of large or small molecules in appropriate liquid vehicle with the presence of gelling agent. Gels are generally applied through tropical or mucosal rout[9].

iv) Rectal route:

Rectal route refers to admistration of drug in rectum. Rectal route is not often first choice but becomes the good substitute when oral route is not advisable. In this dosage forms drug is mixed with waxy substances that liquefies when inserted into rectum because rectum's wall is rich in blood supply through which the drug is absorbed readily. Lack of admistration difficulties and low cost make this route good alternative for parenteral route[9].

A **suppository** is a solid dosage form which consists of one or more APIs dispersed in suitable base and molded in particular shape for insertion in rectum for local delivery.

An **insert** is another type of solid dosage form that is inserted into body cavity (nonsurgical) other than mouth, rectum, vagina etc.

A **medication sticks** are another solid dosage forms generally used for administrating topical drugs.

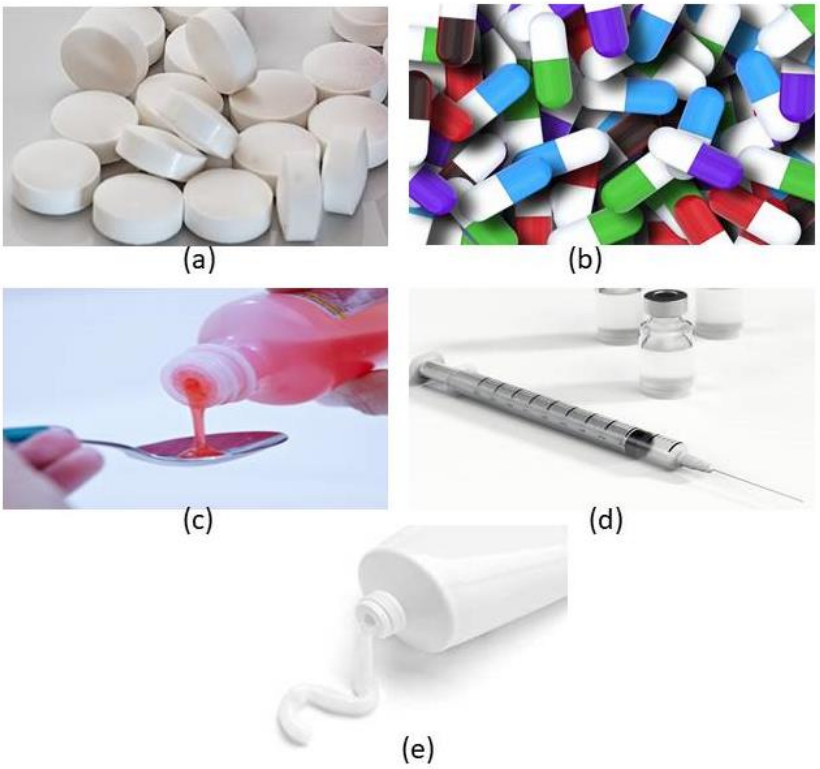

Fig. 1: Diagrammatic representation of (a) Oral route - Tablets (b) Oral route - Capsules (c) Suspensions (d) Parenteral route – Injection (e) Transdermal route- Ointments.

Table 2: Various clinical advantages and disadvantages of different dosage forms and routes of administration in children[10-12].

Admistration and dosage forms	Potential advantages	Potential disadvantages
Oral Solid formulations Tablets Capsules	Better acceptability with liquid and semi-solid food. Easy to administer Dose flexibility	Chance of choking and chewing due to larger size. Limited dose flexibility. Bitter taste of various tablets and capsules. Taste masking requirement of tablets. Risk of direct swallowing.
Oral Liquid formulation Suspensions Solutions Syrups Drops	Most acceptable route in neonates treatment Portability, dosage uniformity Can be used in modified release.	First pass effect. Unable in formation of multi-dose preparation. Device for admistration of drug is critical. Shaking is necessary in case of suspensions. Risks of admistration before suspensions. Less opportunity for the modification in the trend of drug release.
Parenteral Intravenous Subcutaneous injections Intramuscular injections Pump systems	Main route for treatment in neonates in case of emergency. Quick delivery of drug	Unbearable pain while punctuation. Fluid overload Electrolyte imbalance. Incompatibilities with patient. Infection phlebitis, embolism.
Tropical Ointments/Creams Gels Medicated plasters	Painless and easy admistration of drug. Used for the sustained release	Unintended systematic absorption / toxicity risk. Local skin irritation. Ineffective in abundant secretion.
Rectal Suppositories Medicinal liquids	Can be used for very ill pediatric population. Used in the patients who cannot swallow.	Size consideration. Limited bioavailability. Cannot be used in regular stooling pediatrics patients. Cultural and regional ethical barrier.

UNCONVENTIONAL ROUTES OF DRUG ADMISTRATION IN PAEDIATRICS POPULATIONS

To overcome the above mentioned disadvantages of various conventional dosage forms, there is need of development of more age appropriate and patient compliable dosage forms. An initiative of World Health Organization (WHO) ("Make Medicines Child Size") has attracted the attention that the lack of more children compliable medicines has halted the development of children in developing countries[2]. Now there is shift of paradigm for development of adult dosage form to development of more children compliable dosage forms. Various non-conventional pediatric dosage forms are described below.

Children like **confectionary products** a lot. Soft Jelly candies have become very common in children as they enjoy chewing the jelly[10]. Giving medicated jelly proves to good alternative of oral dosage form such as tablets and capsules as chewing jelly also overcome the problem of swelling related problem. Different color and flavor of jellies make the children more compatible toward the dosage form and it also delivers the required therapeutic effect. Hard lozenges offer a slow, unvarying dissolution or erosion over 5 to 10 minutes, not disintegrate, have a smooth surface texture and have a pleasant flavor masking the drug taste[11]. **Effervescent granules** also provide a better alternative to oral dosage form[12]. As children likes effervescent beverages a lot. Keeping these in mind, Effervescent granules containing medicament proves to be more compatible toward pediatrics populations. Effervescent granules of different color and flavor mimics the different type of beverages such as Cola, Mango, Limca *etc.* which make them more popular among the children. These granules are quite stable, flexible in dosing, easy to handle and also of low cost[13]. Compressing these granules under high pressure leads to formation of **effervescent tabs** which also provides the alternative to present conventional dosage forms. Major problems that everyone facing toward the use of tablets and capsules in pediatrics are chance of choking due to larger size of tablets and capsules[14].

Mini tablets prove to be best alternative of tablet and capsules. Tablet of size 4-5 mm are generally considered as mini tablets and there will be no problem of choking even in the children of age less than 1 year. These tablets are quite stable, easy to use, easy to carry and flexible in dosing. Due to high mechanical stability it can be coated easily and also provides the option in sustained release profiling of drug[16]. Various disadvantages of syrup such as in stability issue, expulsion of syrup through mouth, dosing issue can also be overcome through the mini tablets[17].

Medicated Flavored sprinkles are one of the non-conventional and new dosage forms that prove to be good alternative of oral dosage forms. Powdered medicated sprinkles are added with compatible food items prepared in household. It proves to be a successful method for delivering the required therapeutic effect of drug [18]. Various pros and cons of unconventional dosage form are summarized in Table 3.

(a) (b)

Fig. 2: (a) Flvaoored Sprinkles (b) Effervescent tabs in water.

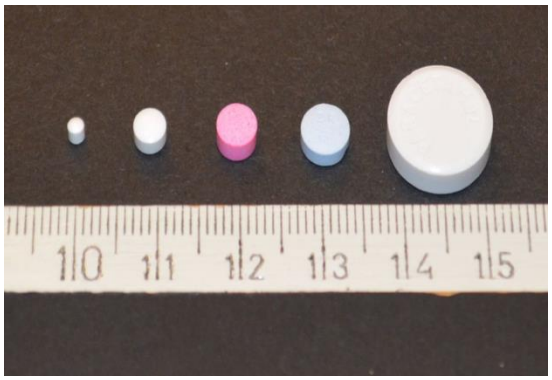

Fig. 3: Comparison of mini tablet of 2 mm and 4 mm with comparison of conventional tablet[15].

Table 3: Various clinical advantages and disadvantages of unconventional dosage forms in children.

Admistration and dosage forms	Potential advantages	Potential disadvantages
Confectionary products Hard medicated candy Soft jellies medicated candy.	Better compatibility with the pediatrics populations. Easy to administer. Overcome the problems related to taste masking of bitter drugs. Used for sustained release Increases the interest of children towards these products.	Chance of choking in case of swallowing. Stickiness due to sugary nature. Issue during the manufacturing of medicated candy i.e. drugs should have high melting points. Cannot be administered in case of diabetic pediatric patients.
Effervescent products Effervescent granules Effervescent tablets	Increases the attractiveness of children due to of mimicking of effervescent beverages. Easy to administer. Dose flexibility, easy to transport and single use product. Can become potential alternative for oral dosage form.	Compatibilities study with most of drugs.
Oral Disintegrating Tablets / Min Tablets / Sprinkles	Easy to administer. Dose flexibility. Can be used in serious ill patients. Overcome the swallowing related problem in patients.	Compatibility with food/ drinks. Intellectual properties cost. Less stable than standard tablets.

CONTRIBUTION FROM AUTHOR'S LAB

Authors have been presently working in Pharmaceutics lab of Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda. Authors and his group have been involved in formulation of non-conventional dosage forms for pediatric patients such as effervescent granules, effervescent tab, Oral disintegrating tablet and medicated candy[19-21]. Effervescent granules containing paracetamol and ofloxacin were developed by author in his lab. Concept of Quality by Design has been applied during the development of effervescent granules. Taguchi Design had been employed for the screening of important factors that can affect quality profile of effervescent granules. Face centered composite design has been employed for optimizing the most significant factors. Effervescent granules were prepared from wet granulation method. Developed effervescent granules were evaluated for various parameters such as Fizz time, Angle of repose, Carr's compressibility index, Hausner's ratio, Bulk density and tapped density. Results found after evaluation were satisfactory and granules can become potential alternative for various oral dosage forms.

Authors lab also involved in formulation of effervescent tab containing paracetamol and ofloxacin. Effervescent tabs were developed by wet granulation and compression method. Developed effervescent were evaluated for various parameters before and after of compression of tabs. *In vitro* dissolution study were also done for developed effervescent tab. Results of developed formulation were found to be satisfactory.

Lab also developed oral disintegrating tablet (ODT) of paracetamol and ofloxacin. Quality by Design is also employed for formulation. FCCD were employed for optimization of significant factors that affect the quality profile of ODT. ODT were manufactured by direct compression method involving marketed co-processed excipients Pharmaburst SSF. ODT were evaluated for various parameters and results obtained were satisfactory. Accelerated stability study for 15 days and 30 days were also done for evaluating the stability of ODT.

Authors also contributed in formulation of medicated hard candy. Hard candy containing paracetamol and ofloxacin were formulated by heat and congealing method.

Author's lab has been continuously involved in formulation of non-conventional dosage forms for pediatrics populations and other types of formulations for treatment of various diseases.

CONCLUSIONS

Medical compliance is critical in all aspects of pediatrics in successful treatment, disease prevention and health promotion. Although various dosage forms such as tablets, flavored suspensions, dispersible/fast dissolving tablets, injections, ointments are available for the children, the problem of non-compliance and missing dose and hence improper medication persists due to various problems related to various conventional dosage forms. Hence there is quest for the development of non-conventional dosage forms for pediatric patients.

In this review, author tried to summarize all the conventional dosage forms available for pediatric population, their potential advantages and disadvantages. Authors also tried to suggest some suitable non-conventional dosage form such as effervescent granules and tab, ODT and medicated candy. Their advantages over the conventional dosage form so that they can be potential alternative of conventional dosage forms. Suggested non-conventional dosage forms has tremendous tendency to attract the pediatric patients towards the dosage forms.

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