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CHALLENGES AND ADVANCES IN PEDIATRIC PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

When we a survey the Indian pharmaceutical market there is huge lack of appropriate pediatric dosage forms that can be administered with concordance to the pediatric patients. In the recent times numerous advances has been taken place in pediatric dosage form development. But still, developing the pediatric dosage form remains a big challenge as it is different from the adult dosage forms in many aspects like, administration methodology, taste masking, drug disposition, safety and toxicity etc. Currently, different technologies are being explored like, orodispersible tablets and oral soluble films have been utilized to prepare the dispersible taste masked drugs for children. Orodispersible tablets by 3D technology is being introduced to incorporate the large doses of drugs. A solid dosage pen device that can administer the required size of extrudate or solid tablet is available. Medicated dosing straw and mini-tablets dispenser have also been developed for convenient administration of pediatric drugs. Further, nipple shields containing the taste masked drugs to be delivered during the milk feeding are being used. Therefore, in the present review article various challenges and advances in pediatric pharmaceutical dosage forms have been reviewed briefly.

KEY WORDS

Advances, Challenges, Concordance, Formulation, Pediatric Dosage Form.

INTRODUCTION:

The field of medicine that is concerned with the health of infants, children, and adolescents; their growth and development; and their opportunity to achieve full potential as adults. [1]

Nearly 80% of drugs available in market for adults are not labeled for pediatric use. [2]

Children differ from adult in many aspects including rate of gastric emptying and pH, GIT permeability, surface area for absorption, capabilities for drug administration, medicine related toxicity and taste preference.

Pediatric patients require different oral drug delivery systems than other subsets of population due to their continuing development. The pharmacodynamic and pharmacokinetic profile of a drug varies depending on the developing stage of child. The largest deviation from adult pharmacokinetics is observed in first 12 to 18 months, where organ functions are developing.

Drug formulation should be adapted considering needs to suit a child's age, size, treatment requirements, physiological conditions. Palatabilty and ease of swallowing are also considered for acceptability of medicines intended for children.

The numerous criteria considered for pediatric formulations are as follows

- Factors related to efficacy and ease of use
- Patient safety
- Factors influencing access of patients to medicine. [3]

In recent years there has been an increased focus on development of various technologies for preparation of pediatric formulations, these are not available in suitable formulation for use in infants and children

This has resulted in noticeable increase in formulation design approach

Example: dispersible tablets, oral films mini tablets

Administration devices: mini tablet dispensers.

The international conference of harmonization divided childhood into 5 age groups

- preterm new born infants
- term new born infants (0-27 days)
- infants and toddlers (1-23 months)
- children (2-11 years)
- Adolescent (12-18 years). [4]

Given below information contains an overview on oral formulation for infants, children including advantages, disadvantages of oral formulations and the age groups they are likely to be used.

CHALLENGES IN PEDIATRIC DRUG DELIVERY SYSTEM

Lack of pediatric drug formulations for both currently marketed and new drugs continue to be a challenge including pediatric formulation development, research and development of more pediatric dosage forms.

The goals of any such research must be the unlimited availability of pediatric acceptable dosage forms.

A. AGE RELATED FACTORS

Formulation acceptability differs across age groups as children gradually develop their cognitive and motor skills and improve their ability to swallow medication. [5]

Taste may be critical to ensure children acceptability because children have low tolerance for disagreeable taste.

Taste preference may differ between children and adults as children prefer sweet flavours and dislike bitter and mint flavour.

Children require dosage forms adapted to their ability and need for variable dose with age/weight

- Age appropriate formulation are Dosage form which
  - can deliver variable doses
  - delivers an accurate dose
  - is safe and acceptable to the child
  - is matched to development and ability
  - avoids medication error. [5]

MAJOR ISSUES

Figure i: Size of various solid dosage forms.

At what age can a child take

1. TABLETS/CAPSULES

Table 1: Size of tablets or capsules according to age

2. ORAL VOLUMES

Table 2: Volume of oral volumes to be taken according to the age

1. TABLETS/CAPSULES

Age group	Acceptability
3-5 years	3-5 mm
6-11 years	5-10 mm
12-17 years	12-17 years
18 years and above	>15 mm

Table 1 Size of tablets or capsules according to age

2. ORAL VOLUMES

Age group	Volume(max)
0-3 years	5 ml
4-12years	10ml

Table 2 Volume of oral volumes to be taken according to the age

B. MEDICAL ADHERENCE

For many years children have been described as "therapeutic orphans" since availability of appropriately formulated medicines with information on their safe and effective use in children has been limited by the ethical and technical difficulties. The development of age-appropriate pediatric formulations, particularly those suitable for young children, presents challenges

with only limited knowledge available on the acceptability of different medicines and how this affects medication adherence. [6]

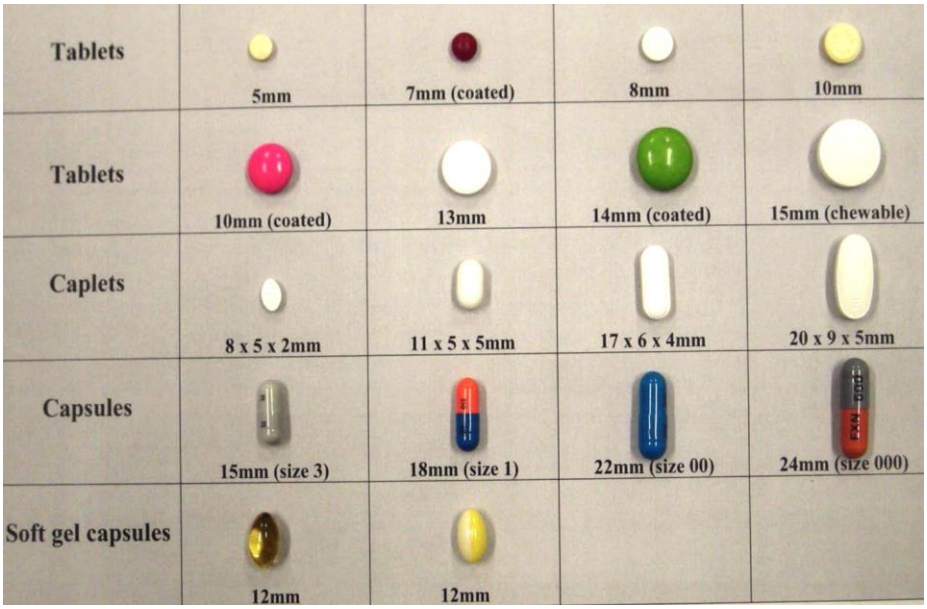

Figure i : Size of various solid dosage forms.

Figure ii: Non-medical adherence.

The term "medication compliance" is defined as the extent to which the patient's action matches the recommendations of the prescriber. The term "medication adherence" is defined as the extent to which the patient's action matches the agreed recommendations of the prescriber.

No matter how effective medication regimens are, if children and parents do not follow instructions adequately, then healthcare is compromised.

Poor medication adherence can have serious consequences for children. Despite recent advances in the development of pediatric medications, the new pediatric formulations are still only a small part of the full therapeutic array needed to serve all pediatric patients and ensuring children get the most from their medications remains an ongoing challenge

- **BARRIERS TO ADHERENCE**

Figure iii: Barriers to Adherence.

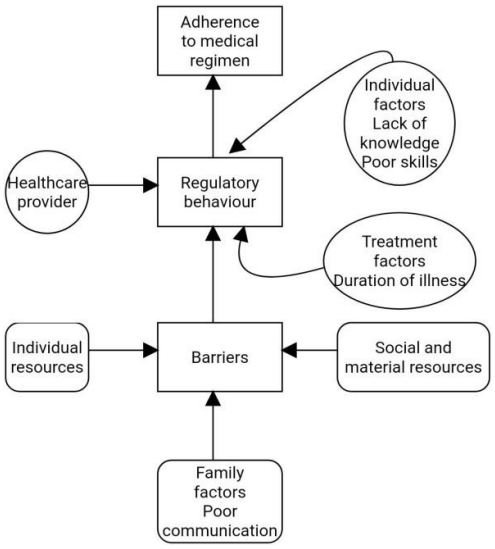

Figure iii: Barriers to Adherence.

Formulation acceptability and preference facilitate medication adherence in children, are important factors in achieving the intended treatment outcomes. Formulation acceptability differs across age groups as children gradually develop their cognitive and motor skills and improve their ability to swallow medications.

The oral route is generally the most frequently used and preferred route of administration for children, but the development of palatable oral pediatric formulations that can be easily swallowed can be challenging.

Children have a low tolerance for disagreeable taste, the use of tasteless or sweet tasting medications can minimize resistance and improve adherence.

Liquid formulations are often seen as the most acceptable dosage form for children and have the advantage of dosage flexibility. However, often the volumes to be administered are so small they can be extremely difficult to measure accurately and can cause confusion for parents. The use of the non-oral route of medication can be useful but poses other issues such as difficult administration/ application, inadequate technique or local irritation.

For inhaled medication, the use of compliance aids, such spacer devices, can improve drug deposition to the lungs. Ensuring continued use of preventative medications, such as steroid inhalers, in children can be difficult as parents often discontinue these medications when their child feels better thinking that this will prevent adverse effects associated with use of the medication. [6]

Figure iv: Various physiological challenges.

➢ IMPROVING MEDICAL ADHERENCE

1. Strategies to improve adherence in children include: using simplified drugs regimens (ideally once-daily regimens are preferred)
   - pleasant tasting medicines
   - liquid or other non-solid dosage formulations
   - regular phone contact between parents and physicians
   - provision of medicines information
   - counseling

2. It is important to involve the child in decisions surrounding medication choice and regimen. Healthcare professionals must take into account the child's understanding and capacity to make independent decisions and the roles of their parents in the therapeutic partnership.

3. While traditional oral dosage forms will be suitable for the majority of patients, in some cases orodispersible or dispersible tablets, granules, mini-tablets, transdermal patches, and controlled release preparations can offer opportunities that may be more acceptable. [6]

4. Prescribers can support medication adherence through a number of means such as
   - dose rounding for ease of administration
   - selecting regimens that avoid the need for multiple daily dosing or dosing at school.

C. PHYSIOLOGICAL CHALLENGES

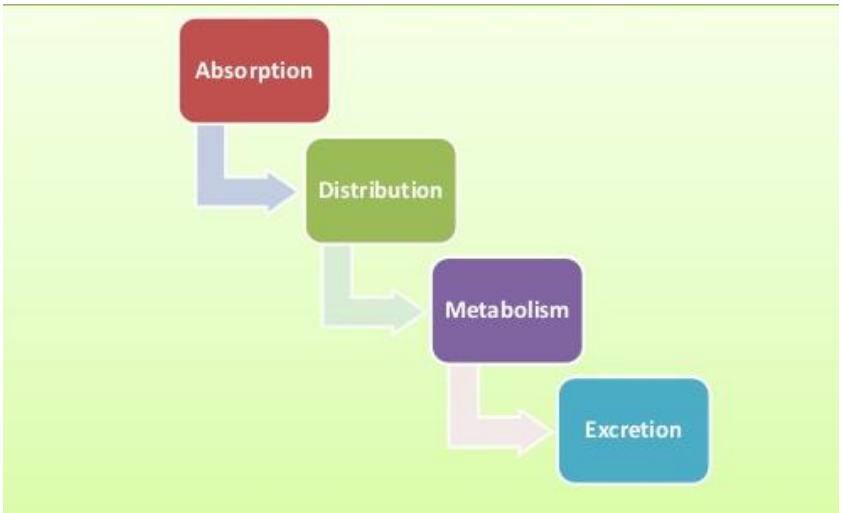

Figure iv: Various physiological challenges.

1. ABSORPTION

Early neonates (2 weeks) are in a state of achlorhydria where the gastric emptying acid production in stomach is absent. This may significantly hamper the therapeutic efficacy of orally administered drugs which requires acidic media for drug release and absorption. Altered gastric emptying in neonates is irregular, unpredictable and prolonged.

They have protracted rate of gastric emptying which results in delayed absorption of medicaments through intestines which may increase drug degradation due to prolonged contact with gastric contents.

Pancreatic enzyme activity is initially low but develops gradually and affects drugs bioavailability which depends on these enzymes. Absorption via non-oral routes is different in pediatric patients since their skin surface area is thrice that of adults relative to weight thereby increasing drug absorption applied topically.

Further the skin is more hydrated and thinner than adults with increased hydration allows deep drug penetration but may result in increased the systemic absorption and toxicity. Neonates have low concentrations of bile acids and lipase, which may decrease the absorption of lipid soluble drugs. [7]

2. DISTRIBUTION

Infants have high ratio of total body water than adults (94% in foetus,78% in full term infant, and 60%in adults) generating a large volume of distribution for hydrophilic drugs and low volume of distribution for lipophillic drugs.

Infants have decreased level of albumin, modified protein binding characteristics and increased competition for binding endogenous substances. Tissue permeability, perfusion rate, tissue drug binding are major factors affecting drug distribution. Decrease in liver volume, regional blood flow of liver reduces drug. [7]

3. METABOLISM AND ELIMINATION

Drug metabolism is substantially slower in infants compared with older children and adults. Less maturation of various pathways of metabolism within a infants. Enzyme cytochrome P-450 present in liver is extensively involved in drug metabolism.

The process of glomerular filtration, tubular secretion and tubular reabsorption determine the efficacy of renal excretion. This process may take several weeks to 1 year after birth to develop fully.

Glomerular filtration rate is about 2-4 ml/min/1.73 m2 in terms of infants. [7]

D. OFF LABEL AND UNLICENSED USE OF MEDICINES

Pediatric drug development is associated with numerous challenges including methodological and ethical requirements for pediatric trials, high developmental cost.

As a result of these challenges there have been only limited research efforts to adapt medicines according to pediatric needs. Thus, only one-third of all medicines are licensed for use in children. The pediatric market has focused mostly on a limited number of therapeutic areas such as anti-infectives, hormones and medicines for respiratory and central nervous system.

Meanwhile there are hardly any dermal preparations and medicines specifically aimed at younger age group for cardiovascular system, cancers and sense organs.

Moreover, especially in younger children and neonates, even authorized pediatric medicines may not always be

age appropriated with respect to dosing, suitability of dosage forms and excipients. These lacks pediatric formulations often leaves health care professionals no alternative but to use adult medicine in and off label or unlicensed manner. [3]

E. DIVERSITY

It is a word that means something different to each and every person. The changing demographics and economics of our growing multicultural world and the long-standing disparities in the health status of people from culturally diverse backgrounds have challenged health care providers and organizations to consider cultural diversity as a priority.

However, health care providers must realize that addressing cultural diversity (includes family organization, language, personal space, health care belief, spirituality, religion etc.,)

Figure v: Cultural Diversity in health care services

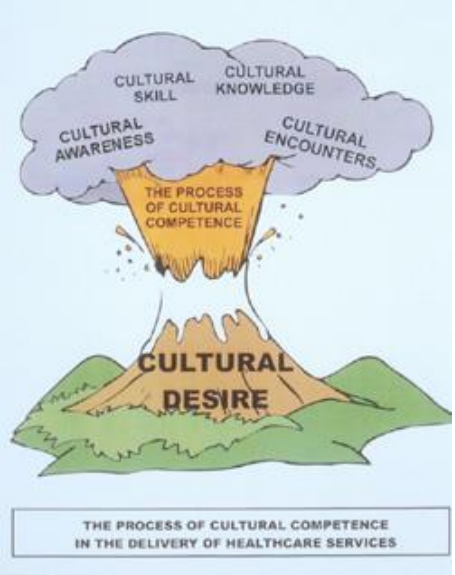

Figure v: Cultural Diversity in health care services

In addition to racial classification and national origin, there are many other faces of cultural diversity. Religious affiliation, language, physical size, gender, sexual orientation, age, disability (both physical and mental), political orientation, socio-economic status, occupational status and geographical location are but a few of the faces of diversity.

F. PEDIATRIC DOSAGE FORM

It is a challenge to find a formulation appropriate for all age groups. The main aim should be to cover as wide range as possible with a single formulation. [4]

The guiding principle for selecting pediatric dosage form should be

- As for adults
- The balance of risk: benefit

Desirable features of quality pediatric medicines common to all dosage forms are outlined below

- CONVENIENT, RELIABLE ADMINISTRATION

The administered dose should contain an amount of API adjusted to age and need of children. Pediatric medicines should preferably be presented as formulations that are ready to administer. The need to manipulate the dose should be minimum.

For accurate dosing the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size and in case of liquid forms the dose volume should be accurately measured. [4]

- ACCEPTABILITY AND PALATABILITY

Acceptability depend on variety of factors such as suitability of dosage form for particular age group, dosing device for a liquid medicine, palatability of an oral medicine, dose volume or size to be administered, appropriate packing, clear and accurate labeling etc.

Palatability is overall acceptance of taste, flavor, smell, dose, volume or size and texture of medicine to be administered. The dose form should not become too attractive to the child in order not to increase risk of accidental poisoning. [4]

- MINIMUM DOSE FREQUENCY

Instruction on the dosing frequency is based upon the pharmacokinetic and pharmacodynamic properties of API but it may be influenced by design of dosage form. Frequent dosing i.e., more than twice daily may impact compliance to the dosing scheme for both caregivers and older children, in particular when caregivers is not available, example in school. [4]

- END USER NEEDS

In addition to the acceptability and palatability of pediatric medicine it is important that they are convenient to produce and affordable. It is also important to consider ease of transportation and storage requirement. Storage in a refrigerator is not always possible. [4]

G. PHARMACOGENETICS AND ITS EFFECTIVENESS

The convergence of pharmacology and genetics, which deals with genetically determined responses to drugs. Pharmacogenetics is also concerned with the differences in the metabolism of medications among

children, adults, and senior citizens; men and women; and people with various medical conditions. [8]

Pediatrics pharmacogenetic studies have the capability to improve the quality of medical care for children. Prescribing medications in children has being largely empirical, but by utilizing pharmacogenetic information, pediatricians gain information regarding which patients are best suited for a particular therapeutic agent and which patients may risk for serious potentially life-threatening complications from standard treatment regimens.

Newborns and infants rapidly undergo simultaneous stages of organ growth and demonstrate large variability in drug response and metabolizing capabilities. Dealing with these concerns clinically meant searching out patterns of drug response in relation to age in an empirical manner in order to determine the appropriate therapeutic agent and dose to be administered in pediatric population.

Simplified dosing equation based on relative body size and age were used to calculate pediatric doses as clinicians made assumption that predictable, linear relationships existed between mass and body surface area in infants, children, adolescent and adults. Presently pediatricians combine the knowledge of clinical pharmacology, developmental physiology and professional experience in order to estimate the most accurate and effective drug treatment plans for children.

A primary goal in pharmacogenetic research involves identifying variability in genes that effect drug response in order to individualize treatment strategies. As a body matures it acquires defensive mechanism that provides protection against xenobiotics and infectious agents. pattern of gene expressions, interaction between these products and role these products play in pathogenesis of pediatric diseases may only be relevant and detectable in children at specific point rate. Exposure to toxins or pharmaceutical agents or lack of medical treatment of a particular illness at sensitive periods of development could irreversible disturb the normal maturation of an individual. [9]

Phamacogenetics has several advantages:

1. The genotype of an individual is essentially invariable and remains unaffected by the treatment itself.
2. Molecular biology techniques provide an accurate assessment of the genotype of an individual
3. There has been dramatic increase in the amount of genomic information that is available, this information provides the necessary data for comprehensive studies of individual genes and broad investigation of genome-wide variation,
4. The ease of accessibility to genotype information through peripheral blood or saliva sampling and advances in molecular techniques has increased the feasibility of DNA collection and genotyping in large scale trials. [9]

H. USAGE OF DELIVERY HURDLES

Inspite of technological advancement of novel drug delivery system in the past, several hurdles still must be overcome. Major problem lies in the usage of tablets and capsules which lacks dosing flexibility. They are not suitable for children aged 4years and younger and the strength used for adults is not suitable for children.

Sprinkling of tablet into fluid or food and grinding them usually results in dosing variability. Administration devices such as “pill swallowing cups” have been used to increase the suitability of tablets and capsules.

Syrups and oral solutions are more readily accepted by pediatrics, but they are not acceptable because of long term storage and dosing error. Another limitation for liquid products with regard to patient acceptability is the lack of controlled release formulations resulting in the need to administer multiple doses throughout the day.

Oral formulations can be designed in such a manner that they are solid when manufactured and liquid when administered

E.g. Dispersible tablets and effervescent tablets.

Intravascular and Intramuscular injections are avoided in children because they are painful.

The use of proper vehicle is also a primary concern for paediatric formulations and it should have improved palatability.

EXAMPLE- Milk has been explored as a vehicle in liquid formulations showing potential for solubilizing drugs. Suppositories and rectal fluids can be used in severely ill children or those unable to swallow the medications, but bioavailability of this dosage form is limited. [10]

ADVANCES OF PEDIATRIC DRUG DELIVERY

A. ORODISPERSIBLE TABLETS

Orodispersible tablets are designed to disintegrate in oral cavities within seconds, avoiding the need of swallowing.

The formulation design does not bring an advantage in terms of dose flexibility with respect to conventional tablets, the various dose strength would be required to fulfill the needs of entire population.The use of orodispersible tablets must be clearly stated to avoid medication errors as the formulation retention time in the mouth alters the bioavailability of the drug.

The Palatability can be improved by addition of sweeteners and flavours to the formulation. Coating of drug particles is an effective way of taste masking.

Various approaches for the development of ODT's includes

1. Lyophilisation
2. Direct compression
3. Tablet moulding
4. Flash heating processing
5. 3D printing technology

Lyophilisation and direct compression methods are most commonly used manufacturing methods. [10]

B. PILL SWALLOWING CUP

Swallowing pills is not always easy,special cups and techniques can help you to gulp the pill down with your drink. One of these cups is oralflo which looks like a sipping cup. [11]

It is available to everyone and suitable for adults and children aged 4 years and above.

It has come to the aid of millions of people who otherwise would contine to choke, gag and suffer trying to take a medication. Oralflo is a revolutionary new medical device that helps doctors, nurses, children, parent's seniors and caregivers administer medication in pill form.

It allows the use of to simply drink any size pill safely and naturally, eliminating the need to place a dry pill in your mouth thus eliminating pill taking anxiety.

The unique design ensures that the water and pill mix together in your mouth. So that when swallow reflex takes over, you can ingest the pill easily depending on the pill size one may not notice the pill at all. [12]

Figure vi: Pill swallowing cup.

Figure vi: Pill swallowing cup.

C. CHEWABLE FORMULATIONS

Chewable formulations (chewable tablets, soft chews and chewing gums) are designed to be mechanically processed in the mouth to aid disintegration or dissolution of API.

The various advantages of chewable formulations are

- Water is not required
- Swallowing is avoided
- May be preferred over other formulations
- Disintegration and swallowing is aided by the patients by means of chewing
- Manufacturing and packaging technology readily available
- Sugar based fillers and sweeteners such as mannitol, sucrose and sorbitol are often used to improve palatability
- Chewable tablets are safe and well tolerated in children from age of 2 years
- Soft gelatin capsules modified by the addition of suitable fillers
- Providing the benefit of soft gels avoiding the need for swallowing the capsule. [10]

D. NIPPLE SHIELD DELIVERY SYSTEM

A nipple shield could safely deliver drugs and nutrients to infants during breast feeding without spreading disease. To use NSDS, a mother places the device containing a preloaded tablet insert over her breast before breast before breast feeding.

As her infant suckles, milk passes through the devices causing active pharmaceuticals ingredients (API" s) to be released directly from the tablets into the breast milk and passed to the infant. The NSDS will be preloaded, disposable and will minimize material thickness while maximizing skin to skin contact with the infant.

NSDS provides a unique user informed solution to this challenge and that a range of API's could be delivered to

infants using NSDS such as antibiotics, anti-malarial, anti retrovirals, vitamins, nutrients and probiotics.

Since the sterile device utilizes the human milk as the tablet's dissolving agent potable water is not required to dissolve a dry tablet. [13]

Figure vii: Nipple shield delivery system.

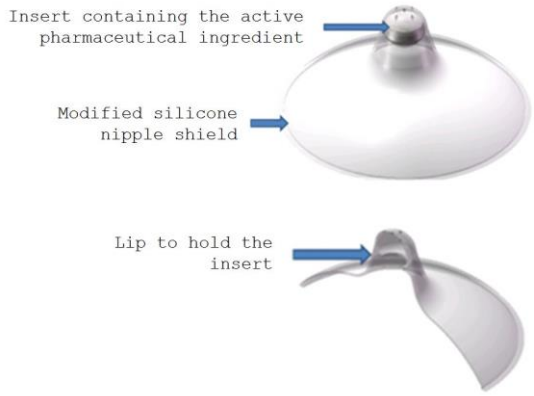

Figure vii: Nipple shield delivery system.

E. MILK BASED ORAL LIQUID FORMULATION.

Various approaches have been utilized to increase the solubility of a drug by modifying its crystallinity and its non-polarity. The various approaches are accomplished by micronization, spray drying or freeze drying.

Approach can be accomplished by modifying the media in which the drug is dissolved.

The modification of the media can be achieved by

- Adjusting the pH
- The use of solubilizing agents(co solvents, surfactants, complexing agents and oil/lipids.)

Milk is a natural, abundant and inexpensive carrier with the desired characteristics for oral drug delivery. In fact, synthetic emulsions are used for oral administration of sparingly soluble drugs, e.g. cyclosporine is formulated as a microemulsion (Neoral®).

Milk, a daily ritual, is an oil-in-water natural emulsion since nearly all of the fat milk is in separate small globules. [14]

The principle behind the approach is to prepare a pharmaceutical composition in order to present the drug in a dissolved form in the gastrointestinal tract, using milk as a dispersing medium and taking advantage of its gastroprotective characteristics.

The following three approaches are utilized:

- Preparation of a solution of an ionized acidic lipophilic drug in an alkaline buffer
- Preparation of a water–ethanol solution of a unionized lipophilic drug
- The use of a small water volume (≈20 ml) for the preparation of a drug solution of a moderately water-soluble drug from an effervescent tablet. [15]

F. 3-D PRINTED ORODISPERSIBLE TABLETS

This 3-D technology will allow large dosing of medication that has the benefit of being fast melting, thereby providing a new option for patients struggling to swallow.

3D printing refers to a manufacturing technique known as additive manufacturing in order to construct 3D models layer by layer, a principle that lead to the discovery of Zip Dose technology and eventually, the highly porous Spritam. Formation of a fully functional Zip Dose begins with mixing a powder blend to make the first layer. After uniformity is ensured, a binding fluid is precisely deposited on top, adhering it to the next layer. This process repeated several times resulting in a highly porous, orodispersible medication. When introduced to infinitesimal traces of water, the bond between the powder and the aqueous fluid deteriorates and disintegration occurs on average in 11 seconds. [16]

Figure viii: 3-D printing orodispersible tablets

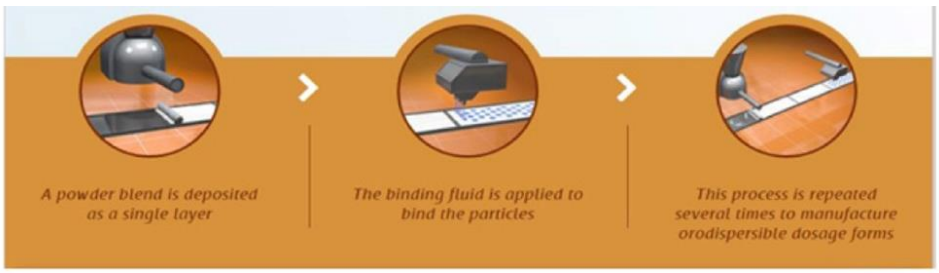

Figure viii: 3-D printing orodispersible tablets

G. SOLID DOSAGE PEN DEVICE

Solid Dosage Pen (SDP), a novel dosing device for individual therapy enables the flexible dosing for oral individual therapy for various targeted groups and with broad range of applications. Solid Dosage Pen have been manufactured by wet extrusion process.

The SDP can be used for the placement of these extrudates dosage selection is carried out via an adjusting screw. Finally, individual dosed tablet-like slices can be cut off the extrudates and can be administered directly. [17]

Figure ix : Solid dosage pen device.

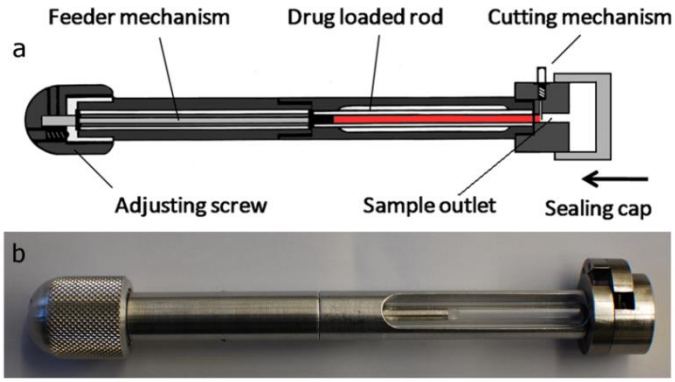

Figure ix: Solid dosage pen device

H. MINI TABLETS

Figure x: Mini tablets

figure x: Mini tablets

Mini tablets are of 1-4mm.

- **2mm**

They may be coated or uncoated which when placed on tongue results in immediate release of drug. Mini tablets can be used from age of 6 months or above.

It requires the use of tablet dispenser.

- The advantages of mini tablets include
- Easy to swallow
- Flexible dosing
- Can be stored outside the refrigerator
- Good portability
- Several tablets can be taken with a jelly as a single dose
- Tablets better accepted that syrups. [18]

- **4mm**

These can be given by parents at home they show immediate release of drug, can be given to children from age of 1 year or above.

Advantages includes

- Better accepted than syrup, suspension, powder
- No need of tablet dispenser. [18]

I. MEDICATED SPOON THAT FORM ORAL PULP

It is an automated compounding concept consisting of pulp like carrier, microencapsulated drug and a dispersing robot by which a pharmacist can deliver any dose.

Oral formulations may be designed in a form that is solid upon manufacture yet liquid upon administration. The formulation characteristic is that it can be released immediately and can be used in new burns also.

Advantages of medicated spoon that form oral pulp includes

- It is easy to swallow
- It is easy to handle

Figure xi: Medicated spoon that form oral pulp

Figure xi: Medicated spoon that form oral pulp

J. MEDICATED DOSING STRAW

A child is ill but doesn't want to take his/her medicine, because the liquid is bitter or the large tablet hard to swallow**.** It enables the administration of granulated medication, since it is already precisely pre-dosed in a straw. The patient tears open the sealed single pack, takes out the straw puts it into his favorite drink, takes off the end cap and sucks. The straw contains a so-called controller, which goes up when drinking the medicine. Once the total dose is taken, the controller stays at the top.

RAUMEDIC has all the machines and tools that are necessary for the fully automated production and packaging of the plastic components. Liquid drugs can also be dosed easily and individually. The system has a double function: The product offers individual dosing as well as easy intake by means of a drinking straw. The user can adjust the dosage prescribed by the doctor by using a dosing ring with defined stages. This personalized adjustment allows an individual treatment for each patient, as required in today's modern medicine. [19]

Optional features include disposable funnels for filling the straw with the correct dosage of medication, funnels which are capable of attaching to pill crushers, removable caps for straws with premeasured doses of medication that prevent medicine loss during handling or storage, flexible necks for ease of use, and flexible straw walls to allow crushing medicine tablets within the straw. [20]

Figure xii : Medicated dosage straw

K. ELECTRONIC MINI TABLET DISPENSER

Automated Pill Dispensers are designed for controlled dosage release when medicine is required at various times during the day. Automatic pill dispensers are particularly useful for people with Alzheimer's, dementia, cognitive problems, forgetfulness, confusion or dexterity complications. They provide peace of mind at medication time by delivering only the next dose at the alarm time. [21]

The Automatic Medicine Dispenser is working for pills and capsules of any size. It has been found that the dispenser can be programmed for 31 days for 21

different medicines. It has the facility to send alarms four times a day. It is possible programmable to dynamically change the number of times and the number of pills to be picked as per requirement.

Figure xiii: Electronic mini tablet dispenser

Figure xiii: Electronic mini tablet dispenser

L. ORAL DISPENSOR COUPLED TO BABY BOTTLE

A medicine dispensing apparatus outwardly resembles a traditional nursing bottle assembly. The bottle has an internal but open-ended receptacle to hold medicine, and the nipple has an integral tube to connect the receptacle to a nipple outlet hole to dispense the medicine. Simultaneous dispensing of the medicine along with the liquid inside the bottle is obtained. A syringe fits inside the receptacle and allows regulated dispensing of medicine.

A nipple is secured to the top of the bottle. A receptacle is formed within the bottle body, and extends axially along its length from the bottom of the bottle towards the open mouth of the bottle.The nipple of the present invention includes a tube which connects at one end at least to one of a plurality of openings in the discharge end of the nipple. The other end of the nipple tube is formed to engage the top end of the bottle receptacle. Therefore, when the nipple is secured to the bottle, the top end of the bottle receptacle is coupled to the corresponding bottom end of the nipple tube. This allows medicine from the receptacle to flow out the discharge end of the nipple, and into the mouth of the infant. [22]

Figure xiv: Oral dispenser coupled to baby powder

Figure xiv: Oral dispenser coupled to baby powder

M. ORAL SOLUBLE FILMS

ODFs are fast disintegrating thin films having an area ranging from 5 to 20 cm^2 in which drug is incorporated in the form of matrix using hydrophilic polymer. Active pharmaceutical ingredient can be incorporated up to 15 mg along with other excipients i.e., plasticizers, colorants, sweeteners, taste masking agents, etc. Plasticizer increases workability, spreadability and flexibility of films thereby reducing the glass transition temperature of polymers.

The thin oral strip which is placed simply on the patient tongue, instantly wet by saliva the film rapidly disintegrates and dissolves to release medicaments. [25]

The administration of ODFs has numerous advantages and some of them are as follows:

1. Easy transportation. [23]
2. No risk of choking. [24]
3. Convenient and accurate dosing. [23]
4. No need of water for administration. [24]
5. Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
6. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability. [24]

Figure xv: Oral soluble films

Figure xv: Oral soluble films

N. SUSTAINED RELEASE SUSPENSION

"Sustained-release dosage forms" as used in the present invention to define a release profile of an active agent over an extended period of time. The terms "modified-release", controlled-release", "prolonged-release", "extended-release", "sustained-release" and "delayed release" are used

Sustained release oral liquid suspension dosage form for once daily or twice daily administration, preferably once daily administration of present invention in general comprises active ingredient in particles, granules, pellets, beads or micro particles which would be additionally mixed with appropriate additives such as viscosity modifying agents that provide suspending properties in the liquid dosage form, sweetening agents which would mask undesirable taste and feel of active ingredient, glidants which provides flow properties and also prevents caking when present in liquid composition, and also other additives such as buffering agents, lubricants, surfactants etc.[26]

CONCLUSION

Safe and effective pediatric pharmacotherapy requires careful consideration of selecting type of drug, suitable dose and age appropriate formulation. During the past two decades an important number of age appropriate products have been developed. Key aspects includes the development of dosage forms such as orodispersible tablets, mini tablets, milk based oral liquid formulation, oral soluble films, child acceptability and importance of suitable dosing devices (pill swallowing cup, nipple shield delivery system, solid dosage pen device). The 3D technology also allows large dosing of medication for patient's struggling to swallow. Even though numerous advances has been taken place in pediatric dosage form development. But still, developing the pediatric dosage form remains a big challenge. However, the acquired knowledge is useful for developing acceptable pediatric dosage form to some extent.

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