

● CASE STUDIES AND SUCCESS STORIES ON PAEDIATRIC FORMULATION

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- Over the past 20 years, the USA FDA has been one of the first regulatory agencies that take steps toward better paediatric formulations. The total number of paediatric formulation available only account for a small proportion of full pharmacologically plethora required to effectively treatment for paediatrics(0 -18 days, months or years).At currently(1)there are a various factors that make paediatric medication errors and potential complications for administration and availability of different dosage forms.(2)
- Paediatrics are field of medicine that are deals with a physical,social,and mental health from birth to the end of adolescence(3)
- Historically ,the goals of studies of drugs for the infants, children and adolescents are protection of children from medication toxicity and providing a long term effectiveness of paediatric formulations(4). The “Drug Efficacy Study Implementation Program’ ’are conducted between 1938 and 1962,highlighted the need of clinical trail and pharmaceutical guideline for drug approval. Since then, effect have been raised to achieve the currently implemented the framework the composed of drug discovery and development (D \$ D),pre clinical studies(phase 0)and clinical studies(phase 1 to 4).(5)
- PROGRESS IN DEVELOPING PAEDIATRIC DRUG FORMULATIONS- New Frameworks for the development of paediatric drug formulations –
- To overcome the challenge a new paediatric regulatory environment has been created to stimulate the development and availability of age-appropriate medicine for children(6). The last year avidecesses in shortages of several significant key medicines and other other products for the paediatric patient.(7)To guide the efforts toward play a significant role in increase the therapeutic benefits for children, the US and European Union government agencies have produced a essential medicines lists, highlighting areas with off-label use in children and gaps in paediatric data collection.Simultaneously,there has been comprehensive WHO activities in improvement on use of safe and appropriate paediatric medicines. The structured framework is based on the three predetermined criteria for each paediatric formulations:1 product efficacy and ease to use (e.g.-acceptability of drug, dose flexibility),2 patient safety(e.g.-stability, risk management, safety of excipients) an 3 patient access (e.g.-affordability,predictability,developments).This individualised approaches to optimal formulations can also be replicated in clinical steps if the selection criteria include in relevant aspects of patient care and safety,(6-7)
- Novel oral formulations-

- Novel paediatric formulation are effectively and consistently improving in the safely use of drug by reducing the barriers of drug administration in children(8). Novel oral formulation such as Mini table and orally disintegrating tablets(ODTs, orodispersible tablet can “define as solid dosage forms that disintegrate in few seconds with the saliva when placed upon the tongue”) can be a conventional solid dosage form in order to provide easier flexibility and not cause a Swallowing problems in paediatric usage, in addition, it was in studies that even ,1 month-old children could be accept and use 2mm diameter mini tablet much more easier then syrups.(9)
- **Chewable tablets (CTs)-**
- Chewable tablets are a system that can be chewed prior to swallowing or without demanding water, though they require dentition. It was suitable for children older than 2 years. Also they will masking the taste to attain high patient compliance. The bioavailability are depends on the chewing pace and strength.ex.-HIV-didanosine chewable buffered tablet, allergy-cetirizine, and asthma-montelukast for children above the age 2 years, respectively, are commercially available.(10)
- **EXAMPLES OF PAEDIATRIC FORMULATION SUCCESSES-**
- The Best pharmaceuticals for children Act(BPCA) and the paediatric Research Equity Act (PREA) are mainly responsible for the encouragement for paediatric medicine formulations.(11) Currently, limited number of paediatric formulation are available specifically licensed medicine for administration for infants, children and adolescents. Some of them are recommended for different age groups patients, some of the recently FDA approved medicines list are:-

Name of drug	Dosage form	Application	Age to given
Ixekizumab	injectable	Plaque psoriasis	Moderate-severe
Crisaborole	ointment	Atopic dermatitis	3 month<2 years
SulfadoxineSofosbuvir	oral tablet	Chronic hepatitis	>6 years old
Vilazodone HCL	oral tablet	Depression	>6-17 years(12)
Ondansetron	ODTs	Nausea/vomiting	2-11 years
Amoxicillin	suspension	Bacterial infection	2-9 months
Vitamin D	syrup	Deficiency of vit.D3	Newborns(13)
Nystatin	oral suspension	Antifungal drug	1 months-2 years
Aresunate+mefloquin	granules	Antimalarial	children-6 months
+pyrimethamine	tablet	Antimalarial	>2 months-18 years(14)
Carbamazepine	chewable tablet	Antiseizure	<6-12 years

Cetirizine HCL/zyrtec	chewable tablet	Allergic rhinitis	2-11 years
Famotidine /Pepcid	suspension	Ulcer treatment	<3 months-16 years
Nitazoxanide/alinia	powder	Antiparasitic drug	1-11 years
Montelukast sodium	oral granules	Antiasthmatic drug	18 month-14 years
Galantamine HBr/Reminyl	capsule	Alzheimer	18 years
Lamivudine/Epivir	oral solution	Hlv/hepatitis	3 month-16 years
Desloratadine/clarine x	syrup	Antihistamine	6 month-12 years
Rimantadine HCL/flumed	syrup	Antiviral drug	<10 years

Ondansetron/zofran	Tablet	Antiemetic	4-18 years
Atomoxetine HCL	Capsule	ADHD	6 years older
Topiramate/chemet	Capsule	Lead poison	Children>18 years(15)
Amoxicillin-clavulanate	Suspension	Cough of PBB	<6 years(16)
Tramadol/doloTRAM	Liquid/Tablet	Pain killer	> 12 years
Colchicine	Tablet	Autoinflammatory diseases	6-12 years Children
Baclofen/ozobaxTM	Syrup	Muscle spasm	0<18 years
Lisinopril/qbrelisTM	Oral solution	Heart problems	6 years and older
Amlodipine benzoate	Tablet	Hypertension	6-17 years
Spironolactone	Tablet	Diuretics	4 day-<18 years(17)

FUTURE DIRECTIONS AND RESEARCH NEEDS ON PEDIATRIC MEDICINE-

- Paediatric research developed by the NLH(national institutes of health),is the largest public funding agency worldwide. The NLH required for reporting on paediatric research

development annually. The COVID-19 pandemic may also place future paediatric medicines research.⁽¹⁸⁾ there was a limited research and development in paediatric medicines, due to the lack of market forces and economic benefits for pharmaceutical industry as compared to adult products. The current situation regarding the formulation and administration of age appropriate medicines for both high and low resource settings are provided to highlight shared and specific key challenges. The WHO is described the dispersible dosage form as well as suppositories and other technologies that may have provide a opportunities for future development on formulations.⁽¹⁹⁾

- **Emerging technologies and approaches-**

- Some of the issues directly related to the formulation have been contributing to paediatric patient non-adherence to treatment, namely the acceptability and organoleptic properties of the formulation, mostly unpleasant taste of APIs. To overcome these issues some of approaches should be used to improved the acceptability and appearance like-
1. nanomedicine for paediatric healthcare- nanomedicine can defined as the use of nanotechnology achieve a nanosize components with specific advantageous properties for formulation of paediatric medicines⁽²⁰⁾

- **3D printing for paediatric medicines-**

- 3DP is a way to fabricate shape t⁽²²⁾

- **Medication delivery devices-**

- 1. X-straw DS technology has works by containing a unit dose of pellets or granules within the straw structure where for a filter pushes the medicine up the straw toward the mouth in response to the sipping drinker. The application of this device may only be appropriate for use in older, toddlers since it required to understanding to drink from a straw.
- 2. ParvuletTM technology is an unconventional technology for the dispersible tablets. It allows for DT or powder drugs to be quickly dispersed (~30s) with very minimum water upon a spoon to form a semi-solid gel consistency, which can be administered directly. This applicable for reducing a dosing error particularly for NTI (narrow therapeutic index) drugs.⁽²³⁾
- 3. Oral drug delivery technology- For the development of paediatric formulation for the children it may essential that are highly quality, ethically researched or approved by the FDA.⁽²⁴⁾ commercialised dosage forms and devices are like orodispersible tablets, oral dispenser coupled to baby bottle, pill swallowing cup, sustained release suspension, chewable soft-gel capsules, easy-to-open capsules. And non-commercialized dosage forms and devices available are- electronic mini tablet dispenser, segmented easy to score tablet, multiple scored tablet, milk based oral liquid formulation, solid dosage pen device, nipple shield drug delivery device.⁽²⁴⁻²⁵⁾
- **MINI- TABLET-** in recent year the regulatory framework supported the design novel technology for age appropriate formulations. mini tablets contain a diameters <3mm with coated or uncoated and orodispersible mini-tablets. they can used in conventional tablets, immediate and modified drug delivery, prolong release or targeted released system.⁽²⁵⁾
- **unmet needs in paediatric medication compliance-**
- The major challenge in development of paediatrics formulation, however the problems associated with administration in population are manifold, because of the highly heterogeneous nature of patient group, rang of new-borns or adolescents and suitable delivery devices for certain formulations. So far, there is a lack of suitable or safe drug for

paediatrics. There was some unmet need in paediatric formulation in orally inhaled drugs and administration techniques which are mainly used for the bronchospasm and anaesthesia(26-27). There will be increased need for more research to develop the novel paediatric forms, and also further investigate the suitability of dosage forms for different age groups. Current advances in paediatric drug delivery such as fast dissolving drug formulation, buccal films and wafers, multiparticulate dosage forms, parenteral choice for children in emergency cases, alternative routes of administration also alternative routes of administration drug delivery systems, a few products are already available on market but others are still under development and need further investigation and clinical proof. For example-COVID-19 medicines, gene therapy tools for brain disease, novel anti inflammatory molecule, CVDs medicines etc.(27)

● The role of precision medicines-

- Precision medicine approaches therapy is also known as the personalised medicine, that Personalised medicine are two approaches to healthcare that aim to tailor medical treatments and interventions to individual patients. These approaches are based on the idea that every patient's genetic makeup, lifestyle, and environmental factors are variability for each person, intended to enhance drug efficacy and safety for individual patients. Precision medicine has the goal to bringing together all sources of variation in drug response to ensure the effectiveness and safety of drugs for a paediatrics.(28)
- Paediatrics does may not deal with miniature men and women, with reduced doses and the same classes of diseases in smaller bodies but it has own independent range and horizon. While there has been dramatic progress in moving in pharmacogenomics testing into the realm of adult medicine this has been less so in paediatrics for many of the reasons. precision medicine also used in cancer treatment .Oncology is work in understanding the impact of genetic variation has been to reduce the risk of adverse drug reactions which a major issue during the therapy- while maintaining therapeutic efficacy(29). The some of the examples of precision medicines-cancer-
 - 1-Thiopurines(6-mercaptopurine,6-thioguanine),Platinums(cisplatin,lobaplatin),
 - 2-vinca alkaloids(vinblastine,vinflunine).
 - 3-Streptococcal infections-prontosil sulfanilamide,antibacterial drug-penicillin. Molecular Therapy-(vismodegib,TB-403,selumetinib)
 - 4-Radiation therapy-has been used for treatment of childhood brain tumors.Precision child health (PCH) is an emerging branch of precision medicine that focuses on the unique needs of the paediatric population. A PCH approach has the potential to enhance both quality of care and safety for patients(30).

CONCLUSIONS-

The development of age-appropriate pharmaceutical products is challenging due to the combined demands of industry, healthcare providers, caregivers and patients. During the past two decades an important number of age-appropriate products have been investigated, developed and patented, and some have gained marketing authorization. The current strategies for the

preparation of age-appropriate oral drug delivery systems have been reviewed throughout this manuscript.

Unfortunately, the limited information available regarding acceptability and patient preference of emerging dosage forms (i.e., ODTs, ODFs, chewable formulations, multiparticulates and mini tablets) for the different age subgroups hinder the rational selection of one formulation approach over another. Owing to the diversity of the paediatric population and the discussed limitations of the current technologies it seems unlikely that a single formulation approach will be acceptable for all paediatric patients. The selection of a suitable formulation approach for a targeted population group needs to be carefully considered for each individual product. Further investigation in this field is desired to allow correlation between formulation technological aspects and patient acceptability that guides such a selection process.

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