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A STUDY ON THE VARIOUS FACTORS THAT AFFECT PEDIATRIC FORMULATION AND THE WAYS TO OVERCOME IT

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ABSTRACT

Because of moral issues and the heterogeneous pediatric population, the development of drugs for children has been disregarded during the twentieth century. There aren't many drugs designed and tested specifically for children, with 43% of centrally authorized pharmaceuticals having pediatric potential but not being approved. To provide age-appropriate pharmaceuticals, evidence-based information is necessary, as are factors such as tailored doses, acceptable bioavailability, non-toxic excipients, uncomplicated administration, and a dependable production technique at a fair price. Pediatric patients require particular oral medicine delivery procedures, as well as compounding and modification. Oral liquid formulations are critical for administering medications to children, ranging from babies to teens. 90% of doctors believe that drug taste and palatability are the most significant treatment barriers, making flavor masking the primary strategy. Children with cystic fibrosis and asthma are given pulmonary formulations, whereas those with systemic and local illnesses are given rectal formulations. Nasal formulations are chosen for their convenience and rapid start, although there is no definitive data on how well children take capsules over tablets. A new regulatory framework has been developed to encourage the development of medications, particularly those designed for children. The current compensation schemes, however, cannot support the development of non-patent medications. To accelerate pediatric pharmaceutical development, companies should identify gaps, increase transparency, improve PIP applications, and resolve ethical problems**.**

Keywords: Pediatrics, formulations, excipients.

2. INTRODUCTION

The development of medicines for children has been a neglected area since the 20th century. Initially, ethical reasons prevented children from participating in clinical research. However, the heterogeneous pediatric population presents challenges in study design and lower returns on investment for companies. As a result, a paucity of medicines designed and studied for children exists. At the end of 2006, 43% of centrally authorized medicines had potential pediatric use but were not approved. The development of age-appropriate medicines for children requires understanding their preferences, physical and biochemical differences, and the complexity of dose adjustment. Children are not just small adults in drug therapy, and growth and development are not readily apparent in adults. There is a need for evidence-based information to guide formulations suitable for children and young people. Ideal pediatric formulations should consider factors such as minimal impact on the child's lifestyle, individualized dosing, sufficient bioavailability, non-toxic excipients, convenient administration, and a robust production process at minimal cost. [1]

A special oral drug delivery method is needed for pediatric patients because of their continuing development and dose requirements. Because conventional formulations are not made for this patient population, compounding and manipulation are necessary. Pediatric patients require age-appropriate oral medication administration devices that promote compliance and concordance. It is difficult to create a formulation that is age-appropriate because there are so many different pharmacological and clinical factors at play. A drug's pharmacokinetic and pharmacodynamics characteristics change as a child develops; thus, it is necessary to adjust the dose to meet the needs of all age groups. [14]

Children, who have different tastes and swallowing abilities than other subsets of the population, require medicines that are palatable and simple to swallow in order to be accepted. Dependence on caregivers affects how well medications are administered and tolerated. Aspects of production, processing, and packaging must be taken into account to guarantee quality and price. It is desirable to strike a balance between emerging technology and patient access to medications. To create formulations with various active pharmaceutical ingredients (APIs), dose strengths, and/or release patterns, flexible technology platforms are necessary. With an emphasis on commercialized products and technologies, recent years have witnessed a surge in formulation design methodologies and administration/dosing devices. [14]

The Best Pharmaceuticals for Children Act (BPCA) and the Paediatric Research Equity Act (PREA) aim to promote pediatric medication studies by increasing the number of clinically tested medications and ensuring their availability in appropriate formulations and doses. However, many therapeutic medicines still lack pediatric-friendly dosage forms. Legislative decisions by the BCPA and PREA benefit pediatric research and labeling, but they can be outweighed by existing medications. Developing pediatric formulations, particularly for young infants, is challenging due to a lack of data on dosage forms, administration volume, dosage form size and taste, and formulation safety. Factors such as dosing, disease processes, study design, and placebo response. [5]

2.1. DEFINITION

2.1 a. Pediatrics

Pediatrics' is a medical specialty that deals with the growth, treatment, and illnesses of newborns, young children, and teenagers. Children's medication suited for their age is a medication that is appropriate for usage in the target age group(s) due to pharmaceutical design.[3]

2.1. b. Pediatric formulation

The ingredients of a specific dosage form of a drug intended for Pediatric usage. [3]

2.1. c. Pediatric medicine / Pediatric medicinal product

The container closure system comes with a pediatric preparation, any measuring or administration equipment, and the user manual. [3]

2.1. d. Paediatric preparation

paediatric formulation in a certain strength (for example, tablets of 5 mg or a solution for injections containing 5 mg/ml), as well as the contents of the marked container for paediatric formulations intended for single use (for example, a solution for injection containing 5 mg/ml, where 1 ml is equal to 5 mg or 2 ml is equal to 10 mg). [3]

2.1. e. Pharmaceutical design of a medicine

A medicine's composition, dose form, administration method, frequency of administration, packaging, measurement or administration tool, and user instructions. [3]

2.2. CLASSIFICATION OF PAEDIATRIC AGES

Class Age	Group
Neonate Birth	27 days
Infant and Toddlers	28 days to 23 months
Children	2 to 12 years
Adolescent	16 to 18 years

2.3. TYPES OF PAEDIATRIC DOSAGE FORMULATION

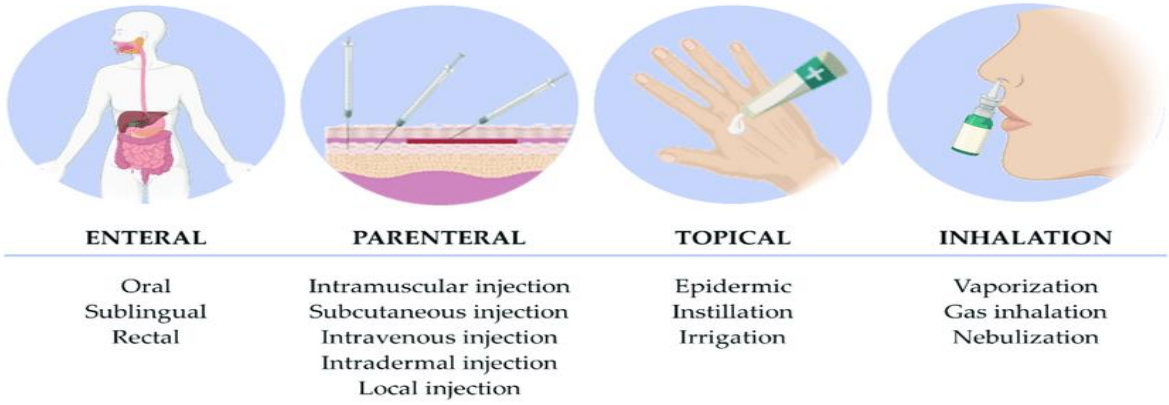

Fig: 1 Preferred route of drug administration of Pediatrics' Formulation

2.3. A.ORAL DOSAGE FORMULATION

1. Tablet Formulation
2. Capsule Formulation
3. Oral Liquid Formulation
4. Sustained Release Formulation

2.3. B.Parenteral dosageFormulation

1. Injection formulation

2.3.C.Topical formulation

1. CutaneousFormulation

2.3. D.PulmonaryFormulation

1. Nasal Formulation

2.3. E.Enternal Formulation

1. Rectal Formulation

2.3. A.ORAL DOSAGE FORMULATION

1. Tablet Formulation

Tablet formulations typically contain 5 to 10 percent of the active substance, 80 percent inactive ingredients, and 10 percent compounds that promote dissolution in the digestive tract. Tablet size and shape are crucial for a child's swallowing ability. [11] The acceptability of tablets among target age groups should be justified and supported by studies or clinical evidence. Training and instructions for co-administration with semi-solid food can improve tablets' acceptability for chronic diseases. Small tablets with a fraction of the

required dose can improve acceptability and dosing flexibility. If a dose requires multiple tablets, the acceptability of the required number should be discussed and justified for the relevant target age group(s). [3]

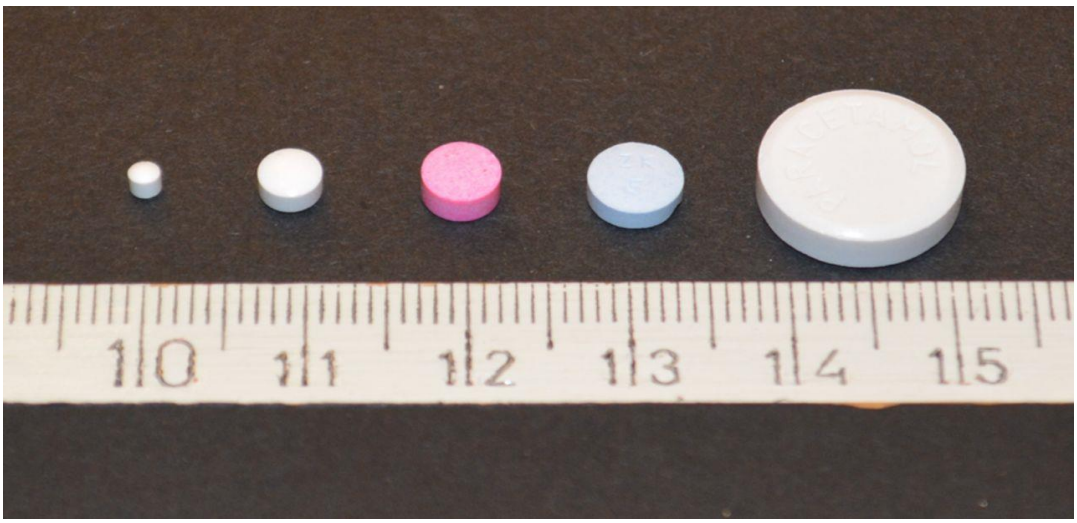

Fig: 2 Tablet formulation of different size

2. CAPSULE FORMULATION

Capsule Formulation Capsules involve encasing the active substance in a “shell” made with a gelling agent that dissolves in the stomach. Capsules should be taken intact, but hard capsules can be opened if feasible, provided the contents meet the same requirements as normal granules. [11] Discuss and justify the suitability of capsules for all target age groups. Limited data exists on capsule size acceptability in different pediatric age groups. Consider capsule size and associated risks when taking intact capsules. [3]

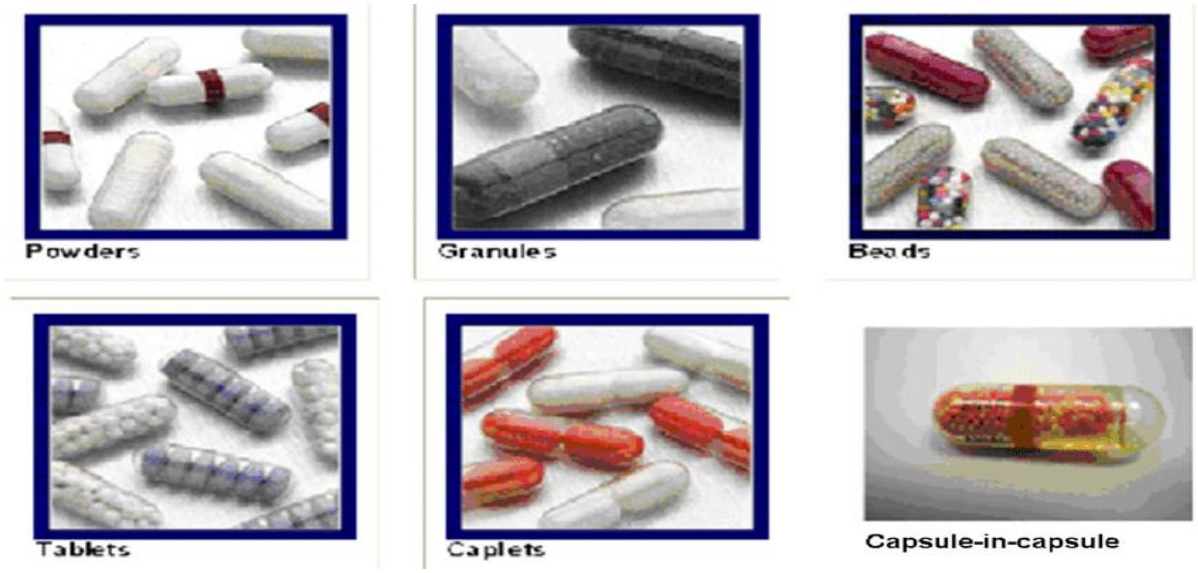

Fig:3 Different types of capsule

3. Liquid Formulation

Oral liquid formulation Liquid formulations are faster and less expensive to develop, and they often have better bioavailability than other oral formulations. The bitter taste of drugs is believed to have evolved as a deterrent against ingesting toxic substances. Liquid formulations, including solutions, suspensions, elixirs, syrups, drops, and emulsions, are preferred for their dose flexibility and ease of swallowing in the lower subsets of the pediatric population. [17] These formulations allow administration throughout the entire population, from neonates to adolescence. [13] The major barrier to developing oral liquid formulations is taste-masking, as 90% of pediatricians in the US reported that drug taste and palatability were the greatest barriers to treatment. [16]

Complex formulations are required to encapsulate drugs with taste-concealing properties. Excipients used in the development of a product need to be safe and acceptable for use by children. [18] The maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years. [12]

Fig: 4 liquid dosage

4. Sustained Release Formulation

Sustained release formulations can be tablets or capsules. They are meant to release a drug into the system more slowly. Sustained-release Pediatric dose forms are meant to release medication slowly and gradually over time, offering a more regulated and longer therapeutic impact while lowering dosing frequency. These formulations are especially beneficial in pediatric patients because they promote adherence to therapy and reduce medication concentration variations. Tablets or capsules for pharmaceuticals such as methylphenidate and some antiepileptic treatments are common examples, as are Sustained-Release Liquid Suspensions for some antibiotics, Transdermal Patches for pain relief or attention issues, and Osmotic Pump Systems for particular instances. Pediatric dose changes are critical to ensure that the formulation is appropriate for pediatric patients, with dosing

determined by the child's age, weight, and individual medical condition. Careful monitoring is essential to ensure that the youngster takes the correct dosage at the proper time.[12]

2.3. B.PARENTERAL FORMULATION

Formulation for Injection These formulations can either be injected or directly administered to the mucous membranes (i.e., nasal drops). They can either be liquid or lyophilized (freeze-dried). The most frequent method for administering active drugs to children, especially those who are critically ill and clinically unstable, is intravenous. The choice of injection depends on the desired therapeutic outcome, the properties of the active ingredient, and the child's acceptability. Considerations for the child's acceptance should include the route, injection location, quantities, pace, viscosity, pH, buffering, osmolarity, needle thickness, and length. The measurement device's precision determines the minimal dose amount, which should be justified in light of the child's age. The right dose rates should be taken into account, as some parenteral preparations may be used in emergency situations. Only neonates may take modest doses of medication to prevent volume overload and allow for vital hydration. Pharmaceutical development should look at issues with compatibility, osmolality, unsuitable diluents, and potential over- or under-dosing owing to lag-volume effects in IV fluid lines.[3]

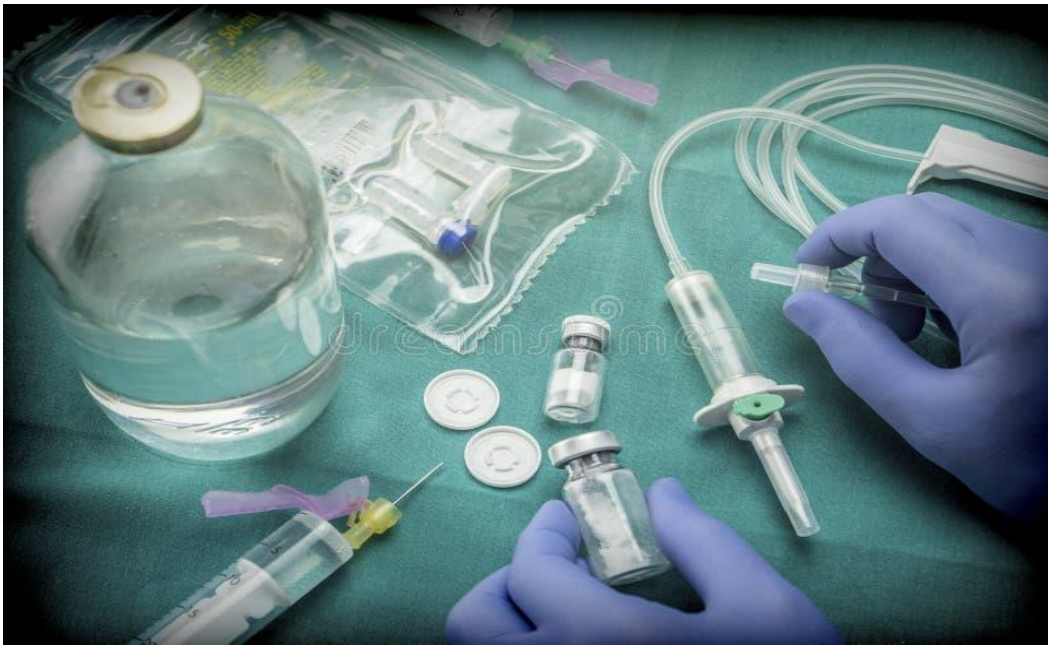

Fig no: 5 Parenteral formulation

2.3. C.TOPICAL FORMULATION

1. Cutaneous Formulation

Skin-Based Formulation Cutaneous formulations are substances that are applied topically to the skin, such as creams, ointments, gels, powders, pastes, and transdermal Consider developmental changes in skin barrier function, such as dermis thickness, epidermis moisture, and body surface area to weight ratio, when creating cutaneous and transdermal pediatric treatments. [11] Use skin-sensitizing excipients and talk about how occlusion, fever, and thermal heating affect skin permeability and overdose. Avoid regular routines by

tailoring transdermal patches and medicinal plasters to the child's size and form. To obtain lesser dosages, create patches and medicated plasters without cutting; nonetheless, some varieties may be created for cutting. Cutting is only permitted when clearly defined lines and constant dosage homogeneity are shown. [3]

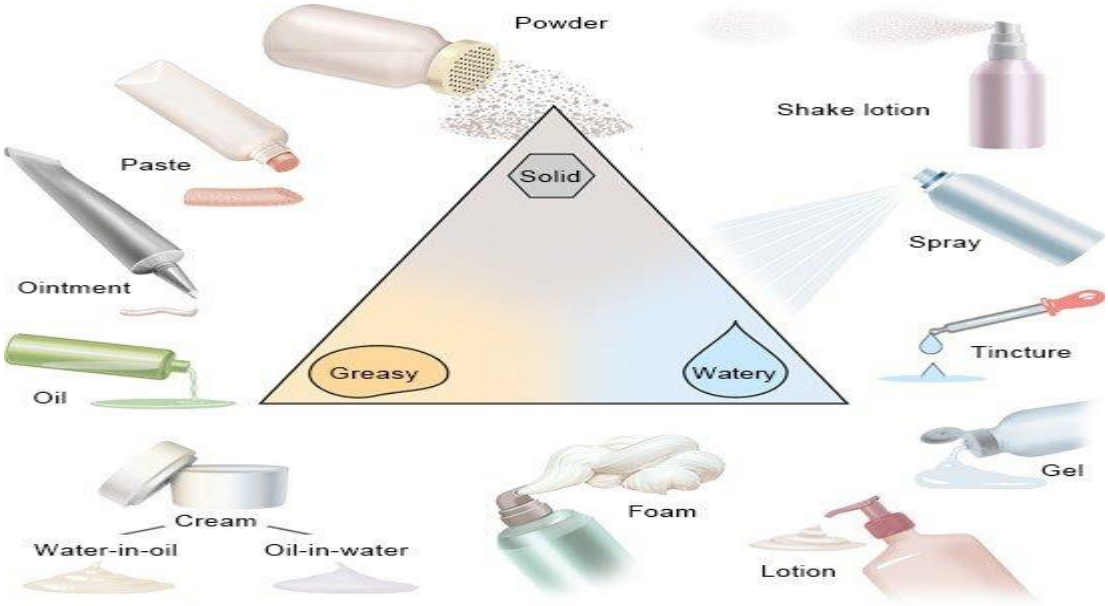

Fig no: 6 cutaneous formulation

2.3. D.PULMONARY FORMULATION

Infants and young children with cystic fibrosis and asthma frequently use inhaled medicines. During the first several months and years of life, breathing habits, respiratory rate, and airway size all vary substantially. In pediatric populations, delivery devices are identical to those used in adult populations, but they can be changed by fastening a small infant- or child-sized mask. Age, device tolerance, and patient preference all play a role in interface selection. Young children who are unable to use dry powder inhalers or metered dosage inhalers (MDIs) may benefit from the use of nebulized liquids. [12]

Fig no: 7 pulmonary formulation

1. NASAL FORMULATION

Pediatric nasal formulations are a practical means of giving drugs to children since they are easy to give and have a quick effect. They are designed with the child's age, weight, and preferred prescription type in mind, such as nasal sprays, drops, or gels. Preservatives and additives are carefully chosen, taking into account any sensitivities or allergies. The pH and osmolarity are suitable for nasal delivery and are suitable for pediatric usage. To make the formulation more pleasant, flavoring agents may be added, but they must be safe and well-tolerated. To prevent contamination, sterility is maintained throughout the formulation process, especially for young patients with weakened immune systems. For pediatric usage, a suitable container and applicator are selected. Patients are educated on optimal placement and dosage procedure.

Fig no: 8 Nasal formulation

2.3. E.EnternalFormulation

1. Rectal Formulation

Rectal treatments, frequently administered as creams, ointments, suppositories, foams, sprays, and enemas, are used to treat both local and systemic illnesses in children. They are helpful in situations of nausea and vomiting, upper intestinal diseases, and for newborns and kids who have trouble swallowing oral medications. Age-related changes in the rectum's diameter, length, and volume occur about the time when a person reaches adulthood (10 years). Dose modifications for paediatric patients are often made based on body surface area, weight, or height. Paediatric suppositories are normally made at a size that is suitable for children; however, there is little evidence on their accuracy or stability. Following the same guidelines as adult medications, paediatric dosage forms for rectal administration are created.[12]

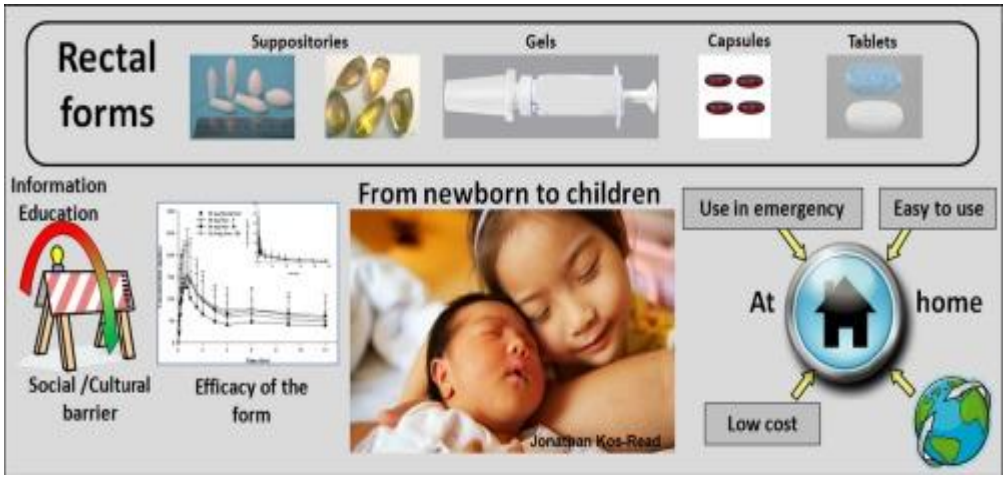

Fig no; 9 (Rectal formulation)

2.4. Pediatrics dosage forms advantages &disadvantages

Table no: 1 Advantage and Disadvantages

SNO	Administration and Dosage forms	Potential Advantages	Potential Disadvantages
1	Oral, Liquid preparations Suspensions	Main Router For(long-term)treatments in children Acceptability from term birth maximum dose flexibility	First-pass effect Instability of Multidose preparations Age-appropriate dosing volume for full-dose ingestion(5<5ml in younger and <10ml in older age groups)
2	Solution,Syrup,drops Powders and Granules for reconstitution	Stability, Portability, Good dosage uniformity option for different doses and modified release	Dose measuring device critical
3	solid dosage forms Tablets Capsules,Powders,Granules,Sprinkles,Multiparticulates,Mini-Tablets Or dispersible/chewable preparations	Better acceptability(with liquid/semi-solid food)Dose flexibility Ease of Administration Can be used in neonates and seriously ill infants	Shaking for dose accuracy(suspensions) Incorrect dosing for oral drops(Critically of dose) Risks of administration without prior dispersion/dissolution Ability to swallow intact dosage forms
4	Administration through nasogastric Tubes		Risks of chocking and chewing limited dose flexibility Dose-measuring devide needed compatibility with food/drinks Limited control over dose intake. Taste-masking requirements Less stable than standard tables Risk of direct swallowing Intellectual properties costs Ease of administration and dosing accuracy (Volume,density,viscosity,particle size) potential compatibility with feeding tube material Doses and rinse volume relevant to target age group Relevant size of feeding tubes
5	Parental Intravenous injections	Main router for neonates and emergency case Quick/high/constant blood and tissue drug concentration	Infections, phlebitis, embolism fluid overload, electrolyte imbalance
6	Subcutaneous injections	Sustained -release preparations	inappropriate diluents Measurement of dose Volumes
7	Pump Systems		Lag-volume effects in intravenous line small veins, punctuation pain, needle phobia incompatibility with coadministered intravenous medicine Drug migration into plastic tubes(plasticizer desorption of phthalates from circuits)
8	Rectal	Can be used in severely ill children or those unable to swallow	size considerations
9	Suppositories		Limited bioavailability(minor absorption area, lack of active drug transporters, smal fluid volume for dissolution)

10	Rectal Liquids		Frequent stooling in brreast-fed infants, uncontrolled defecation in infants Lower compliance and concordance cultural regional acceptance barriers
11	Topical Transdermal	Provision of constant blood levels	Unintended systemic absorption/ toxicity risk in neonates(large skin surface area, thickness, hyderation, perfusion
12	Transdermal patches	painless and easy administration of bolus	
13	Medicated Plasters	Sustained drug delivery	Natual barrier for penetration of many drugs safety of excipients Local skin irritation deliberate removal of patches/plasters
14	Nasal	Good nasal trans mucosal bioavailability	Unwanted systemic effect
15	Solutions, drops	needle free access to systemic circulation	irritation of the mucosa
16	Semisolid dosage forms		ineffective in abundant secretion
17	Pulmonary	Avoidance of hepatic first-pass metabolism	increased deposition in upper/central airways(small airway diameter)
18	Metered dose inhaler with Space/facemask	Painless application	Decreased total lung deposition(reduce motor abilities/low inspiration volume)
19	Nebulizers(older children)		Device use critical to improve inhaled doses
20	Dry powder inhalers (older children)		

4.FACTORS AFFECTING PEDIATRICS DOSAGE FORMULATION

4.1. Formulation Related Factors

Infants as young as 6 months can use mini-tablets (2-4 mm). To examine the acceptability of tablets varying in size from 5 mm to 8 mm, children between the ages of 1 and 11 were divided into mixed age groups. The outcomes of these studies provided conflicting evidence for the acceptability of tablets in various sizes for various age groups. [10]

4.1.1.Tablet

4.1.1. a. Size

The acceptability of capsules in children in relation to size has not been reported. Studies in adults show that the esophageal transit of capsules is not affected by capsule size, in contrast to the significant influence of tablet size on its transit. [10]

4.1.1.b.Shape

The acceptance of tablets by kids has not been documented in any studies. Adult studies have shown that the size of a pill affects the shape that patients prefer. Small tablets are typically desired to be arched round, whereas medium and big tablets are typically preferred to be oblong or oval. (10)

4.1.1. c. Film coating

Children were given film-coated and uncoated mini-tablets, and two instances of coughing or choking were linked to coated tablets (V. Klingmann et al., 2013; S. A. Thomson et al., 2009). However, there aren't any direct comparisons between coated and uncoated tablets in terms of how well youngsters can take them.

4.1.2. Capsule

When compared to a tablet, there hasn't been any concrete comparison of how well children tolerate capsules versus pills. However, due to the potential for the moist Gelatin shell to adhere to the oesophagus, it is advised to take capsules with caution in general. Studies on adults have produced contradictory findings.(10)

4.1.2. a. Size

There is no information on whether youngsters can tolerate capsules of different sizes. Studies on adults demonstrate that, in contrast to tablets, which have a considerable impact on their transit, capsule size has no effect on esophageal transit. (10)

4.1.2. Density

There are no known effects of capsule density on children's ability to swallow. Adult studies have demonstrated that hefty capsules travel through the esophagus much more quickly than light capsules. (10)

4.1.3. Liquid

4.1.3. a.Taste

Numerous studies and reviews have found that flavor is crucial for children's acceptance of liquid medications.(10)

4.1.3.b.smell

A liquid's aroma has been linked to its flavour and may help make liquid medications more palatable. There isn't much information linking medication smell with kid acceptability. (10)

4.1.3. c.Viscosity

We couldn't find any information on how children's acceptance and ease of swallowing are affected by the viscosity of liquid medications. Viscosity is related to patients' perceptions of the palatability of liquids, according to studies in adult populations and patients with dysphagia. Although considered unpleasant, thick liquids may increase the safety of swallowing for people with dysphagia. (10)

4.1.3. d.Texture

Particle size has been linked to the mouthfeel and grittiness of suspensions as well as the texture of a liquid. Children's acceptance of things has not been the subject of in-depth research. (10)

4.1.3. e. Volume

Liquid medication dosages should be able to be swallowed whole. According to research done by D. V. Jones and C. E. Work in 1961, children between the ages of 15 months and 3.5 years ingest on average 4.5 ml of liquid every swallow. Very low oral liquid dosages may contribute to problems with children's dosage accuracy. Solid oral dosage formulations those are flexible. (10)

4.1.4. Multiparticulates

Due to their improved palatability and flexibility in administration, such as when combined with semi-solid food, they are often well tolerated by youngsters. The biggest issues with acceptability in youngsters are grit and mouth feel. Due to the requirement for reconstitution, administration is thought to be time-consuming, which presents difficulties for parents and caretakers. (20)

4.1.5. Dispersible and effervescent tablets

Children between the ages of 3 months and 8 years have been evaluated for the acceptability of dispersible pills. Generally speaking, these are preferable to oral liquids like syrup. For prolonged use, however, the possibility of tooth erosion must be taken into account. These formulations' high sodium content has been linked to an increase in adult cardiovascular events. Children's long-term health impacts have not been researched.(19)

4.2. Rectal FormulationRelated Factors

4.2.1. A .suppositories

Pediatric patients range in age and weight, which may influence the size and strength of suppositories. Formulation is critical for providing correct dose since it must be age-appropriate and simple to deliver. Patient cooperation is also vital, since the child's degree of comfort, fear, and cooperation can all affect the ease and efficacy of administration. Rectal sensitivity changes with age, and certain medical conditions might impair medicine absorption and efficacy via the rectal route. Proper lubrication is vital for

pleasant suppositories, and temperature sensitivity should be maintained according to manufacturer's guidelines. To avoid infection and maintain comfort, suppository delivery requires proper hygiene. Parents and caregivers require comprehensive training in safe and successful administration, including learning the exact method and dose.

Medication compatibility is also important, since certain medicines may not be suited for rectal delivery, although others are. It is critical to ensure that the drug chosen can be provided by suppository and is appropriate for the child's condition. Understanding potential side effects and bad responses to the medicine is critical, and parents and caregivers should be taught about what to look for and when to seek medical attention. Proper storage and handling of suppositories, including temperature management, is critical for preserving their efficacy and safety.(6)

4.2.2. Enema

Pediatric enemas are medical treatments that are used in children to provide drugs, ease constipation, or prepare the intestines for specific medical tests or surgery. To guarantee the safety and efficacy of pediatric enemas, several aspects must be considered.The child's age and weight are the most important considerations. To prevent overwhelming the child's fragile systems, the suitable enema solution and dose should be selected depending on his or her age and weight.

Another important consideration is the enema solution. There are several types of enemas available, such as saline, mineral oil, or soapsuds, and the decision is based on the individual medical requirement and the child's health. It is critical to choose the option that is both safe and appropriate for the youngster. Administering a pediatric enema needs competence and care. To reduce discomfort and avoid harm to the child's rectal region, the healthcare professional or caregiver must be experienced in the operation.

The child's participation and comprehension are important factors in the success of a pediatric enema. Pediatric patients may be fearful or resistive to the operation, and attempts should be made to explain it in a child-friendly manner to allay their concerns. When doing a pediatric enema, cleanliness is essential. To avoid infection, proper hand washing and equipment sterilization are required. Finally, it is critical to keep an eye out for any negative responses or side effects. Caregivers should be trained on what to expect and when to seek medical treatment if difficulties occur during or after the procedure. (6)

4.3. Nasal related factors

4.3.1. NasalSpray

Pediatric nasal sprays are used to treat allergies, reduce nasal congestion, and deliver drugs to the nasal passages. The child's age, medicine kind, and compliance during administration all influence safety and efficacy. Because infants and young children have narrower passageways, choosing a mild and regulated spray is critical. Some nasal sprays contain decongestants, antihistamines, or steroids; therefore, the dose should be changed. To avoid illness and protect the child's well-being, healthcare personnel should use child-friendly procedures and maintain hygiene. It is critical to monitor the frequency and duration of nasal spray use in order to avoid rebound congestion or other negative effects. Parents, caregivers, and healthcare professionals should be aware of potential allergic responses and be aware of when to seek medical attention if necessary. [7]

4.3.2. Nasal drops

Pediatric nasal drops are frequently used to treat a variety of nasal disorders in children, such as congestion, allergies, and infections. Age, weight, type of nasal drops, nasal anatomy, patient cooperation, proper technique, hygiene, frequency and duration of use, monitoring for adverse effects, storage, allergies and sensitivities, and potential drug interactions with other medications should all be considered to ensure safety and effectiveness. Administering nasal drops to children can be difficult, but tactics such as diversion, moderate constraint, and making the process pleasant can assist. [8]

To avoid harm or discomfort, use proper technique by tilting the child's head back slightly and applying the drops carefully. Hands should be cleansed before handling the drops to ensure hygiene and sterility. Observance of the specified dose schedule and length of treatment. [9]

4.5. Parenteral related Factors

4.5.1. Intra muscular

Pediatric medicine is characterized by a complex approach to care and treatment that is impacted by a variety of circumstances. The child's age and developmental stage, weight and growth, emotional and psychological considerations, parental involvement, family dynamics, communication, pain management, vaccination and preventive care, cultural and socioeconomic factors, nutrition and dietary needs, environmental factors, legal and ethical considerations, developmental disabilities and chronic conditions, trauma and abuse, and transition to adult care are all factors to consider. Healthcare practitioners must customize their approach to accommodate age-specific problems, utilize age-appropriate terminology and approaches, and address emotional and psychological issues. They must also evaluate the child's family dynamics, family structure, and support system, as well as communicate diagnoses and care plans in age-

appropriate language. Finally, healthcare practitioners must manage difficult legal and ethical considerations while putting the child's needs first. [10]

4.5.2. Intra Venous

Pediatric doses must take into account characteristics such as age, weight, body surface area (BSA), renal function, and organ system maturity. Understanding the medication's pharmacokinetic and pharmacodynamic characteristics is critical for correct dosage. The IV method provides for quick medication administration, and the dose is determined by the desired therapeutic impact. The medicine composition and rate of infusion are also critical. Providers should double-check figures and engage with healthcare experts to ensure safety and monitoring. To avoid potential problems, other drugs must be compatible. For proper dosage, standard standards such as the Pediatric Advanced Life Support (PALS) guidelines and institution-specific protocols are required. For particular groups, such as preterm newborns, severely sick children, or those with comorbidities, extra considerations may be required. [10]

4.5.3. Subcutaneous

In pediatric patients, subcutaneous (SC) medicine delivery is injecting pharmaceuticals beneath the skin, generally into fatty tissue. The child's age and weight, body surface area (BSA), medication type, therapeutic goal, pharmacokinetics and pharmacodynamics, route of administration, frequency and timing, concentration and formulation, needle size and length, injection site, and patient comfort and cooperation are all factors that influence subcutaneous dosages. Because of their smaller size and metabolism, younger children and newborns may require lesser dosages. Dosing may also be changed based on the child's BSA, medicine type, therapeutic objective, pharmacokinetics and pharmacodynamics, method of administration, frequency and timing, concentration and formulation, needle size and length, injection location, patient comfort and compliance, and so on. Safety and supervision are critical, with doctors double-checking figures and keeping a careful eye on the infant.

4.5.4. Intra atrial

In pediatric patients, intra-articular (IA) medication delivery is injecting medications directly into a joint area for diagnostic or therapeutic purposes. Age, weight, joint size and anatomy, medication type, joint condition and diagnosis, patient size and accessibility, intra-articular volume limitations, pharmacokinetics and pharmacodynamics, anesthesia or sedation, procedure expertise, risks and benefits, monitoring, and consent are all factors that influence intra-articular dosages. Because of their smaller size and metabolism, younger children may require lesser dosages. The amount and distribution of injectable medicine are also affected by joint size and architecture. Pharmacokinetics and pharmacodynamics are important factors in dose determination. In some circumstances, anesthesia or sedation may be necessary. Healthcare practitioners should be familiar with the technique and, if necessary, contact specialists.

4.6. Pulmonary formulation related factors

Pediatric pulmonary care is concerned with the diagnosis and management of respiratory disorders in children, which are impacted by factors like as age, respiratory development, prematurity, weight and growth, congenital diseases, allergies and asthma, infections, and chronic illnesses. Environmental factors such as secondhand smoke, pollution, or allergies can aggravate respiratory diseases, and vaccines are essential for prevention. Pediatric patients require proper sizing and administration of respiratory support devices, drugs, and nourishment. Adherence and results can also be influenced by behavioral and psychological issues, family dynamics, socioeconomic considerations, and cultural factors. Long-term care requires education and self-management. A comprehensive and integrative approach is required, requiring coordination among pediatric pulmonologists, nurses, respiratory therapists, and other experts. It is frequently required to collaborate with pediatric pulmonologists, nurses, respiratory therapists, and other experts.

4.7. Patient Related Factors

The ability of a child to adhere to and accept medication is strongly influenced by their age. Parents' capacity to administer and adhere to treatment recommendations is essential for success in lower paediatric groups. Forgetting, misinterpreting, and not complying are some causes of non-compliance. As they get older, kids take charge of their care, becoming more independent and capable of making choices. Different paediatric subgroups have different levels of formulation acceptance, depending on factors such as immaturity, the development of motor and cognitive skills, developmental changes, disease perception, competency, and biological changes. Specific dosage forms' age-appropriateness should be evaluated based on their acceptability, capability, and appropriate Excipient for each subset. For oropharyngeal dysphagia, postural adjustments are frequently utilized as compensatory therapies, especially to prevent aspiration of thin liquids. Head rotation and chin-down posture are effective postural methods that lower aspiration risk by narrowing the chest cavity. [13]

4.8. Disease Related Factors

The paediatric population's tolerance and adherence to medication regimens might be affected by acute or chronic disorders. Children who suffer from long-term conditions, such as HIV or asthma, begin to learn how to swallow at a young age. However, youth resistance and peer pressure may have a negative impact on adherence. Poor adherence to treatment for chronic illnesses might result from prolonged treatment periods, clinical remission, and increased drug use. Due to toxicity, poor treatment outcomes, and medical issues, non-adherence leads to suboptimal clinical outcomes and increased healthcare costs. [9]

5. IMPROVEMENT OF PAEDIATRICS FORMULATION

Improving pediatric drug formulations is critical for the safe and successful treatment of children. Consider various dose forms, allow for adjustable dosing depending on age, weight, and condition, and design taste-masked formulations with pleasant tastes as strategies. For proper dosage, varied liquid concentrations and user-friendly measurement instruments are required. Child-resistant packaging, stability, and the use of as little preservatives and additives as possible are all safety factors. Compliance tools, such as blister packets with clearly stated dose days and times, can assist parents and caregivers in keeping track of their medication regimen. Education and training should include detailed advice on correct administration methods, storage, and any adverse effects. Improvements can be guided by palatability studies.

Creating a pediatric formulary inside healthcare facilities guarantees that only formulations suited for young patients are prescribed. Collaboration with regulatory authorities to establish and execute pediatric-specific guidelines and rules can motivate firms to engage in pediatric medication research. In patient-centered design, pediatric patients, carers, and healthcare practitioners are involved in the formulation's design and assessment. Investing in R&D can lead to the discovery of novel delivery methods and technologies that improve the safety and efficacy of pediatric drugs. Improving pediatric healthcare and drug management requires a multidisciplinary strategy including pharmaceutical firms, regulatory agencies, healthcare professionals, and carers.[15]

6. FACTORS AFFECTING PEDIATRIC DOSAGE FORMS OVERCOME

❖ Age and Weight Variability

In pediatric patients, age and weight variations have a substantial influence on medicine dose and administration. Developmental changes, cognitive and behavioral abnormalities, and age-related variances in body mass are among these causes. The physiological development of children during childhood and adolescence influences how their bodies metabolize and respond to drugs, including liver and kidney function, enzyme activity, and body composition. These modifications can have an impact on drug absorption, distribution, metabolism, and excretion (ADME). To accommodate for these variations, healthcare personnel must often change medicine dosages based on a child's age, with pediatric dosing standards classifying patients into age groups. Weight fluctuation, on the other hand, has the potential to influence medication concentrations and therapeutic effects. To manage weight fluctuation, healthcare practitioners frequently employ weight-based dosing, which determines the right amount depending on the patient's weight.

❖ **Developmental changes**

The physical, psychological, and emotional development of a kid from infancy through puberty has a substantial influence on their response to drugs. These developments necessitate that healthcare practitioners examine a variety of criteria when prescribing and providing medications to youngsters. Organ maturation, gastrointestinal changes, body composition, cognitive and behavioral development, communication skills, medication administration, understanding and adherence, psychological and emotional states, psychosocial factors, growth and body size, and weight-based dosing are all examples of physiological changes. Children's organs, such as the liver and kidneys, mature as they grow, impacting medication metabolism and disposal. Drug absorption can also be influenced by gastrointestinal alterations, with young infants having slower stomach emptying rates. Body composition changes, such as changes in fat and muscle mass, can have an influence on medication distribution and elimination. Communication development is an example of cognitive and behavioral development.

❖ **Taste and Palatability**

Taste and palatability are important in pediatric medicine because children are more sensitive to the taste and texture of drugs. Understanding these preferences is critical for developing drugs for different age groups and individual differences. Flavored liquids, chewable pills, and orally disintegrating tablets are all options for dosage formulations. Pediatric-specific dose forms are developed by pharmaceutical firms and compounding pharmacies to prioritize taste and palatability while retaining therapeutic efficacy. Natural or artificial tastes are frequently used in flavored pharmaceuticals, however care must be taken to ensure that the flavors used are safe for children. When choosing tastes and sweeteners, sweeteners such as sugar or sugar replacements should be considered. Caregiver education is critical for optimal drug administration, and patient-centered care includes incorporating the child in medication decisions. Allergies and sensitivities should be avoided.

❖ **Pharmacokinetics and Pharmacodynamics**

Pharmacokinetics and pharmacodynamics are important concepts in understanding how pharmaceuticals act in the body, such as absorption, distribution, metabolism, and excretion. These ideas are especially essential in pediatric medicine, since dose and medication response in children can vary greatly due to developmental changes. medication absorption can be affected by factors such as gastrointestinal immaturity, delayed stomach emptying, and medication formulation differences. Dosing can also be affected by distribution, enzymatic breakdown, and elimination. Pharmacokinetic models assist healthcare workers in determining optimal doses depending on variables such as age, weight, and organ function. The pharmacodynamics response can be affected by receptor sensitivity and developmental changes, and juvenile patients may respond differently to drugs. Safety and adverse effects are also critical considerations, and therapeutic drug monitoring (TDM) is required to ensure that drugs are safe and effective.

❖ **Safety Concerns**

Because children are a fragile group with specific physiological and developmental features, pediatric healthcare is critical for assuring the safety of drugs and therapies. Dosing accuracy, adverse drug reactions (ADRs), medication administration, pharmacokinetics and pharmacodynamics, off-label use, pediatric clinical trials, medication storage and handling, allergy assessments, emergency preparedness, medication reconciliation, interdisciplinary collaboration, and regulatory oversight are among the most important safety concerns. Weight-based dosage and pediatric formulations are critical for proper dosing and preventing drug mistakes. Adverse drug responses (ADRs) must be quickly monitored and controlled, and patient and family education is critical. It is also critical to choose age-appropriate dose forms and administration strategies. To optimize safety and efficacy, pharmacokinetics and pharmacodynamics should be studied in relation to age and developmental stage. Collaboration among healthcare practitioners across disciplines

❖ **Lack of Pediatric Data**

Pediatric data shortages in clinical trials and research offer substantial issues in pediatric medicine and healthcare. The main challenges include a lack of data, dose ambiguity, safety concerns, and off-label usage. To address this, regulatory agencies such as the United States Food and Drug Administration mandate pediatric research, design and conduct pediatric clinical trials, extrapolate adult data, monitor drug safety, develop pediatric-specific dosage forms, establish collaborative research networks, provide incentives, and form pediatric consortiums. In addition, ethical concerns, informed consent, and international collaboration are required. By using these measures, healthcare practitioners will be able to make better judgments, eliminate ambiguity in pediatric medicine, and guarantee that pediatric patients receive evidence-based, safe, and effective care. Pediatric data may be used to improve the safety and efficacy of medical treatments for children by encouraging collaboration among stakeholders.

❖ **Formulation Challenges**

Due to the special demands and features of children, pediatric medicine has formulation problems. Palatability and taste, dose flexibility, dosing accuracy, stability and shelf life, allergies and excipients, swallowing issues, needle-free choices, age-appropriate information, bacterial contamination, and pediatric trials are examples of common obstacles. Flavored liquid preparations, chewable pills, orally disintegrating tablets, or taste-masked formulations can be designed to meet these issues. Due to the variations in weight and age among pediatric patients, dosage flexibility is needed. Dosing precision is critical to avoid under- or overdose. With improved components and regular stability testing, stability and shelf life are also critical. Allergens and excipients should be kept to a minimum, and swallowing issues should be addressed. Needle-free delivery, age-appropriate information, and bacterial contamination are all issues that may be addressed. Collaboration

❖ **Regulatory & Ethical Consideration**

Regulatory and ethical factors have a significant impact on pediatric medicine and healthcare. The FDA and EMA's pediatric research guidelines, for example, require the creation of children-specific dosage forms, formulations, and labeling. Medication off-label usage in young patients is prevalent, although regulatory bodies encourage research to broaden these indications. Adverse event reporting is critical for drug safety monitoring. To avoid mistakes, labeling and packaging must offer clear, age-appropriate information. For pediatric patients participating in clinical studies, parents or legal guardians must provide informed consent. Beneficence, autonomy, non-maleficence, fairness, privacy, confidentiality, research ethics, best interests, end-of-life care, ethical committees, and cultural competency are all ethical issues. Healthcare practitioners must emphasize pediatric patients' well-being, respect their autonomy, and weigh the risks and benefits of therapies. Equal access to safe and effective therapies is ensured by justice, while privacy and confidentiality are maintained. Informed permission, low risk, and thorough analysis of possible rewards and burdens are all part of research ethics. Decisions for end-of-life care should be made in the best interests of the patient and their family. Collaboration among healthcare practitioners, researchers, regulatory agencies, and ethicists is vital for ethically and responsibly navigating the intricacies of pediatric healthcare.

7. LIMITATIONS

Pediatric dose forms, which are prescription formulations particularly tailored for children, have unique restrictions and obstacles as compared to adult dosage forms. Some of these constraints are as follows:

- Taste and Palatability: Making medication pleasant for children is one of the most difficult issues in pediatric dose forms. Many medications have a bitter or unpleasant taste, which can cause youngsters to refuse to take their prescription.
- Age-appropriateness: When it comes to dose forms, children of different ages have varied demands. Infants may require liquid formulations, whilst older children may be able to take pills or capsules. It might be difficult to create age-appropriate dose forms.
- Dosage Accuracy: Because of differences in body weight and metabolism among children, ensuring proper dosage for pediatric patients can be difficult. Pediatric dose forms must be properly constructed in order to allow for exact dosing.
- Safety Concerns: Pediatric formulations must be safe and devoid of potentially dangerous excipients or additives. Considerations for allergies, preservatives, and other possible risks are included.
- Stability and Shelf Life: To guarantee that the drug stays effective until the expiration date, pediatric dosage forms must remain stable throughout time. This can be difficult, especially with liquid formulas.
- Compliance: Children may have trouble swallowing pills or capsules, and they may spit out or refuse prescriptions more frequently. This can have an impact on drug adherence and efficacy.

- lower Market: Because the market for pediatric pharmaceuticals is lower than that for adults, pharmaceutical companies may be less inclined to engage in research and development of pediatric dosage forms.
- Lack of Pediatric Data: Because clinical studies involving children are frequently restricted, detailed dose information for pediatric patients is lacking. This can make determining the right dose for different age groups and circumstances difficult.
- Weight-dependent Dosing: Because dosing for children is often dependent on weight, healthcare practitioners must carefully calculate and modify doses to avoid over- or under-dosing.
- Availability: Not all drugs are accessible in pediatric-specific formulations, necessitating compounding or off-label usage, both of which can be dangerous.[2]

8. GlobalPediatrics market analysis

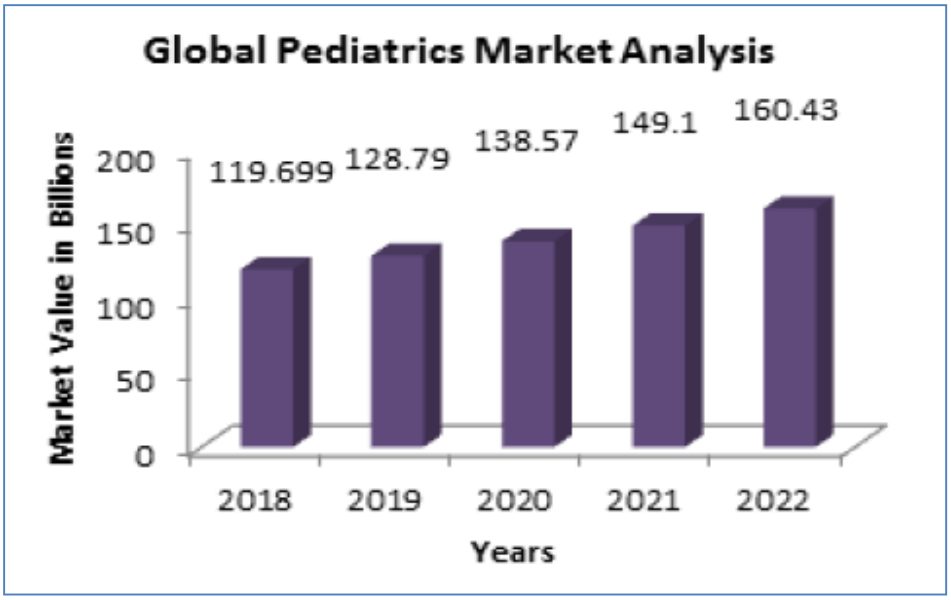

Fig no; 10 (Global pediatric market analysis)

From 2018 to 2022, the global market for pharmaceutical pediatric dosage forms experienced steady growth due to increasing awareness of pediatric patients' unique medication needs and the growing emphasis on pediatric healthcare. Regulatory initiatives like the Pediatric Research Equity Act in the US and the Pediatric Regulation in Europe have encouraged pharmaceutical companies to invest in pediatric drug development, leading to the introduction of a wider range of pediatric-specific medications and dosage forms. Advancements in drug delivery technologies, such as taste-masked formulations and pediatric-friendly packaging, have also contributed to the market's expansion. The pharmaceutical industry recognizes the long-term potential of this market and is actively engaged in research and development efforts to cater to pediatric patients. However, challenges persist, such as the need for more extensive clinical trials, ensuring safety and efficacy, and addressing pricing and accessibility issues. The COVID-19 pandemic has also introduced additional complexities to the pediatric pharmaceutical market. Despite these challenges, the

global market for pharmaceutical pediatric dosage forms is expected to continue growing as pharmaceutical companies, regulatory bodies, and healthcare providers collaborate to meet children's specific healthcare requirements.

9. CONCLUSION

Traditional pharmaceutical development has not prioritized paediatric dosage forms due to challenges in regulations, technology, and industry. Modern technology and taste-masking techniques have made conventional dose forms more patient-friendly. To improve paediatric medicine, new recommendations emphasise product design and innovation. Orally disintegrating films and tablets, especially mini-tablets, offer a viable substitute for drug therapy for young children. However, there is a lack of scientific study on dosage forms and excipients, particularly for young children.[15]

Designing age-appropriate pharmaceutical products is challenging due to the demands of the pharmaceutical industry, medical experts, carers, and patients. More study is needed to correlate technological formulation aspects with patient acceptability. [7] Recent regulatory changes and advancements in understanding paediatric illnesses have increased the demand for evidence of the therapeutic benefits of paediatric therapy. Modelling and simulation can assess the efficacy and safety of innovative drugs, particularly for rare illnesses. Standards should be established to ensure proper application of M&S techniques in children, improving effectiveness and safety. [2]

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