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A Review on Pediatric Dosage Forms and Method's to Enhance its Palatability.

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ABSTRACT:

The Pediatric Dosage Forms Production Requires Intensive care and management.This is because the children(Pediatric patients) are not able to Swallow medicine if taste bitter or any other taste makes it difficult to give medicine to pediatric group patients,New pharmaceutical dosage forms face technical challenges and Thus during the Development Process Requires careful consideration For development pharmaceutical dosage forms. This is an important need for Research and Development in pediatric medicines.Only as malamount of drug utilized for the Therapeutic agents in Children.These therapeutic agents are clinically evaluated.It may not always be possible to provide authorized, commercially manufactured, Age-appropriate,ready-to-adminster prepartions.The ideal Intermediate in terms of assurance of quality and Bio-availability.This compound only distinguishes the experience and skilled Pharmacist. Newly, the care gives manipulated medicines ,for Example, by segmenting tablets in addition to foods or Liquids.Clinical trials recently realized that the investigation of Pediatric medicines in pharmaceutical companies Important.The cost of pediatric product development could Result in momentum have been proposed by the EU and regulatory bodies.Further more some commonlly used excipients May be unsuitable for use in children; and some dosage forms May be undesirable to the pediatric population.

KEYWORDS: Pediatric, Bioavailability, Age-Appropriate, Palatability, Therapeutic Agents, Pharmacokinetics, Excipients.

INTRODUCTION:

There is challenging to give medicines to infants and children's.Children's may not administer medicines for many reasons, Such as fear taste, feeling uneasy or discomfort. Palatability is a one of the important element of patient acceptability. The provision of safe, As well as effective, in pediatric is necessary. The development in safe and effective formulations for pediatric patients is a major challenge as they have different pharmacokinetic and pathophysiolgic conditions as compared to adults. Infants and other children might absorb, distribute Eliminate, drugs in different ways compared to adults. Therefore, medication prescribed for adult and young people is differnt.Drug absorption in childhood is highly affected by changes in accordance with the gastric PH and stomach emptying time. Especialy, at birth gastric PH is neutral and PH is decreases in two to three days after birth.This process continues for week so years still being reached to thebgastric PH of an adult stomach. Gastric emptying time is lower at six to eight month old infants as a result of the immaturity of the neuroegulation of gastric motility. When compared to an adult body the higher amount of water and therefore lower plasma protein in concentration is present. Different drug distribution rates in the organs of a child cause due to this Situation. Another important factor to be considered is the possibility of the presence of metabolic disorders in infants that may result in reduce drug excretion (glomerular filtration, tubular secretion and tubular Reabsorb ion) and prolonged drug half- Life i.e. In childs, new born and infants it's very important Factor effectively determine the Safe and adequate doses of drugs.Thus, its highly necessary to understand the pharmacokinetics of drug and pharmacodynamics Of drug.Thus to improved palatability of pediatric dosage forms various approaches made in order to improve the pediatric medication taking Behavior.

ANATOMY OF PEDIATRIC GASTROINTESTINAL TRACT:

Several routes of administration are possible in pediatric population among this routes the oral route is the mostly preferred. It's Simple, convenient and Diagnostic. After oral administration the drug is Subjected to several Process.The gastrointestinal (GI) tract is an organ system, composed of the oral cavity; esophagus, Stomach and intestines. That helps to transport, digest, absorb and expel.

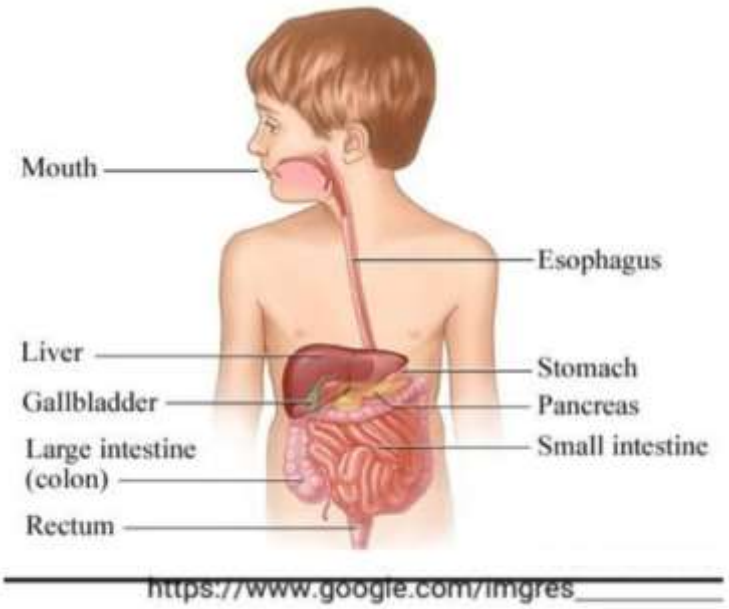


Fig: Gastrointestinal Tract

1] ORAL CAVITY: The first stage of digestion starts from the mouth. Where saliva is excreted to moisten the mouth. In New born, the tongue is Short and broad. Tongue descending in to the or pharynx by the age of 4 years. The larynx is situated at a higher position, while the soft plate touches the Epiglottis.During development, the larynx moves downwards. Pharynx associates with food way and airway. Additionally, the size of the oral cavity would limit the size/volume.

2] ESOPHAGUS: The part of the digestive system which connecting the pharynx to the stomach, allowing the passage of Food for digestion is called as esophagus. The Esophagus measures approximately 25cm long in a mature adult. The Esophagus is a portion of the digestive system connecting the pharynx to the stomach. Serve as transfer drug, food,solution from throat to stomach.

3] STOMACH: In stomach most of the digestion takes place. The shape of stomach is J shaped bag like organ that stores the food temporarily, break sit-down, mixes and churns it with enzymes and other digestive fluids. Finally passes it along to the small intestine. Some absorption takes within the stomach, and majority of the absorption takes place within the small intestines and therefore, gastric emptying and intestinal motility are rate limiting step for absorption. Gastric emptying in new burns and neonates is reduced and variable as compared to adults. Absorption is delayed Due to increasing Gastric emptying time, short transient Time and reduced intestinal absorption surface area. Additionally, the capacity of the stomach also increases with age from 10 to 20mL in Neonates, 20mL in age of 2 years and 150 ml in age of 16 years.

4] INTESTINE:

1] Small Intestine: The small intestine is a structurally coiled thin tube, and its about 6 meters in length, Most of the absorption of nutrients takes place in the small intestine, and also the drug absorb In small intestine. This is due to presence of large surface area of small intestine.In small intestine Food is mixed with enzymes from the liver and the pancreas. The surfaces of the small intestine function by absorbing the nutrients from the food in to the blood stream, which carries them to the rest of the body.

2] Large Intestine: The large intestine also known as the Colon. It is a thick tubular organ wrapped around this Small intestine. Its Primary function is to process the waste products and absorbed any reaming nutrients and water back in to system. The reaming waste is then sent the rectum and Discharged from body as stool.

PEDIATRIC DOSAGE FORM CLASSIFICATION:

[Based Upon Routes of Administration Pediatric Dosage Forms Can Be Classify As Below]

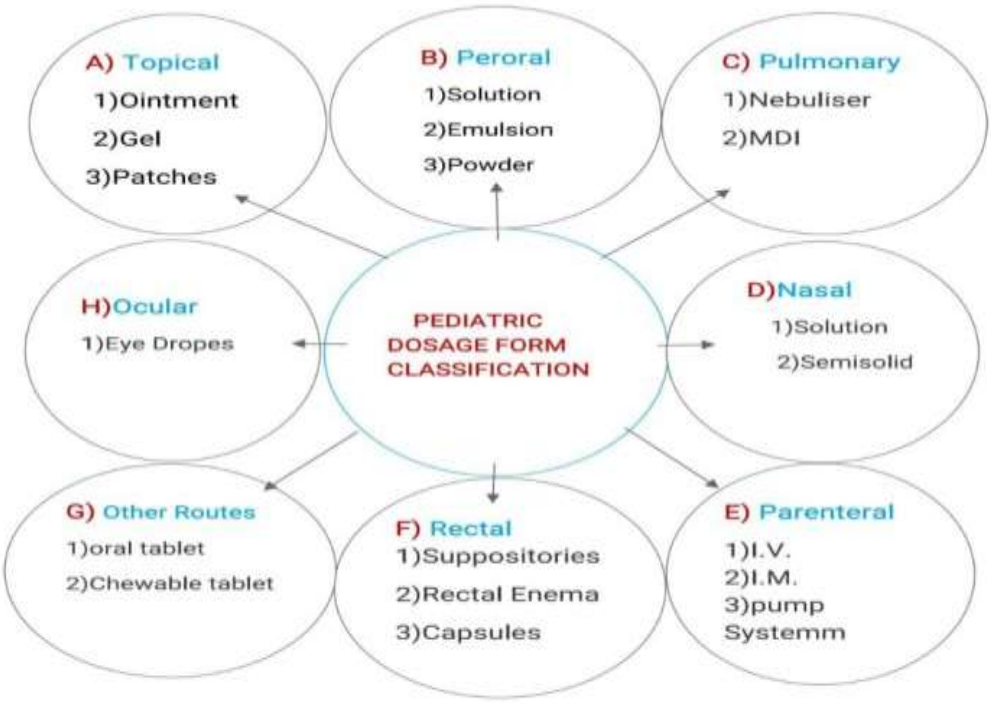


Fig: Classification of Pediatric Dosage Form

1] ORAL LIQUID:

Oral Liquids are Suitable formulation for younger and children because these Is Easy too swallowed and allow for flexible dosing based on the children age and weight. At The time of administration Liquids mixed with different flavors help to mask the taste and Smell of a medicine. However liquid formulations are not without risk. Small volume is required to be measured. Although smaller volumes may be preferable, if the use of more concentrated liquid still may create an additional risk.bOral Liquid is classified as follow:

1) SOLUTION:

Solution is a mixture of two or more substances. With various Accidents were added to the formulation so that the formulation made in such a way that palatable to the children's or pediatric group. This enhances flavour of Formulation and its viscosity in such way that It's easy to swallow by children's. Children are self take medication due to its Sweat or any other flavor percent involution. This makes solution more palatable.

2) SUSPENSION:

Suspension is a liquid Dosage form and it's also improved the palatability of dose. Suspension is a Heterogeneous mixture of two OR more substances in which one phase is dispersed in other phase. The suspension uses various Suspending agent, flavor and Excipentdue to presence of such component It's will become Easy swallowed by children due to liquid consistency not involved problem which associated with respect To solid Dosage forms i.e. difficult To swallow to children.

3) EMULSION:

It's a biphasic system, which is also liquid consistency and viscous, contain API and other Recipients which improved its flavor and its appearance also attract to children's and easily swallowing by them.

2] SOLID DOSAGE FORM:

Alternative for oral Liquid formulations is these solid Dosage form if an oral Liquid is not available. A solid Dosage form requires manipulation i.e. (chewing, crushing, dispersing, breaking) to provide administration. Particular drug properties should be considered :Palatability physiochemical, bile or light sensitive) hazardous drug Release kinetics (e.g. modified release, Enteric Coating).

1] TABLET:

Tablets are suitable alternative to Oral Liquids, particularly when medicines are unpalatable. However, a children ability to swallow tablets must be considered. Tablets should be formulated in such a way that easily swallowed by children. For these the use of small size tablet formulation preferred rather than the large size tablet. The tablets should be colure with various colorants used for formulation of tablet thus this attracts the children towards medicine and improve mint in its compliance.

3] MODIFIED RELEASE TABLET:

Modified-release tablets should be swallowed whole, as chewing OR crushing them may damage them OR differed relapse formulation. Modifications made in such way that swallow Tablet Easily improved children compliance. Modified release dosage forms are advantageous in case of Formulated as a pediatric dosage formg.its serve as medium to give medicine to children who not able to take the bitter medicines. Modified release tablet are modified in the one of more characteristics which leads to formation of tablet which is easy to swallow by children.vModified-release dosage is a mechanism that (Differ from immediate- release dosage) delivers a drug with a delay after its administration or for a prolonged period of time (extended-release or to a specific target in the body. This modified release dosage forms gives there effect for longer time period.

4] CAPSULE:

Capsule is the mostly acceptable Dosage form among other dosage forms. In most of the children's capsule is preferred Rather than tablets. However, capsules Made up of gelatin and have flexibility. Gives stability to coating solid as well as liquid material in to it. As the capsule composed of core which drug is filed and a shell which coats the core. Core prevent direct contact with drug hence improve palatability of dose. Most capsules are formulated to be swallowed whole. Some hard capsules (filed with powder o recoated granules) may be opened and their contents mixed or sprinkle in food. This mask the bitter taste of drug and thus children are Easily Take the medicine without any problems.

3) OTHER TECHNIQUES.

Sprinklers: Sprinkler is a dosage forms which comes under a platform technology. Formulation of children dose is an difficult Task as the children Not taken the medicine which are not palatable thus the risk of developing disease, thus to improve the compliance such type of sprinkler technique used in which the drug which given to the children Is mixed with its food thus drug will enter into body with Help of Food, thus this dosage forms uses an food as A carrier source for transferring drug in to body.

Fig. ***Dosage forms***

PHARMACOKINETIC FACTORS:

1] ABSORPTION:

Absorption is the first physiological process. In which the degree of bioavailability vary significantly due to differences in the development in the gastrointestinal (GI) tract. Factors like surface area Available, intestinal permeability, gastric pH, gastric emptying, GI motility and immaturity of intestinal mucosa, transports System and secretion of bile affect on the Extent of Absorption.

2] DISTRIBUTION:

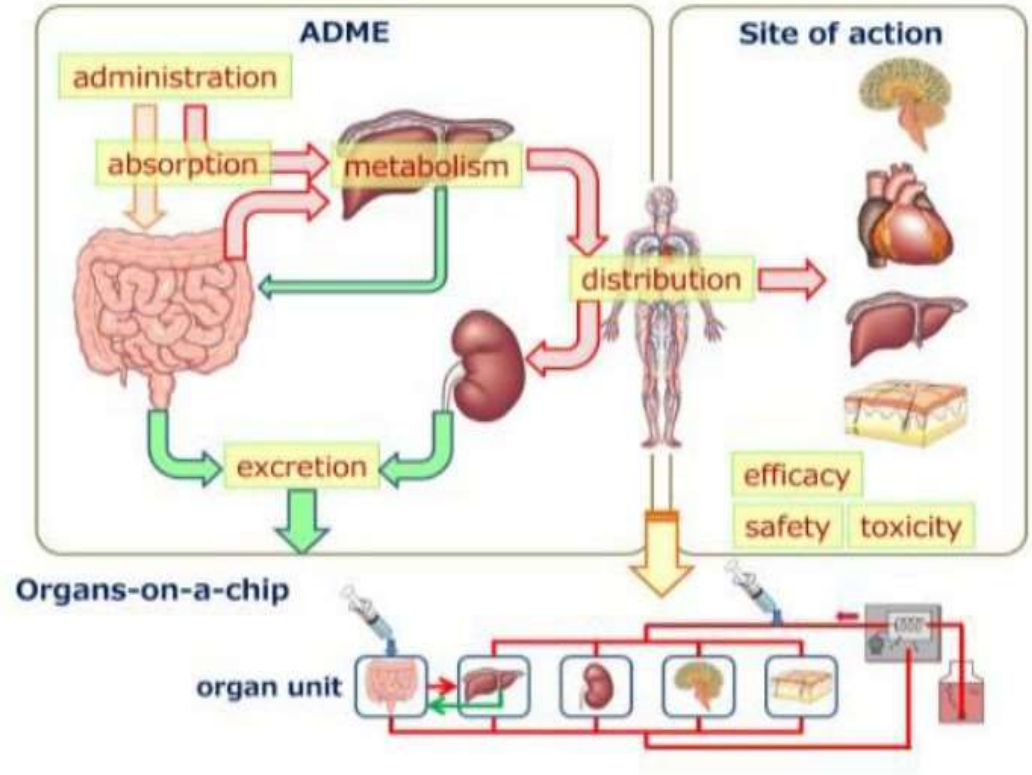
As a child grows and Develops, to available water content (both intra And extracellular) concentration decreases, from around 90% v/w in Neonates and infants, down to 5-60%v/w in adults...The development in the blood brain barrier (BBB) in infants is immature therefore significantly increase the risk of toxicity of subtances. This toxicity occurs due to the high level of drugs enter in to the central nervous System.

3] METABOLISM:

The liver is the organ responsible for metabolism, where drug is metabolized in to rather non-toxic and more water-soluble compounds, reducing toxicity and an excretion via urine and bile. In Neonates, metabolize enzymes are immature. This enzyme leading to suppressed enzyme Expression and activity, it helps to increasing potential for substance accumulation. Through CytochromesP450 (CYPs) Are class of enzymes that serve to metabolize toxic substances and Drugs oxidation occurs. Pharmacologically, substances undergoing high degree of metabolism.

4] ELIMINATION:

Elimination is the process in which the drug/substance and their metabolites are Excreted from the body.Excreation occurs through the kidneys .Determinant affecting the rate and extent of elimination which Includes glomerular filtration rate (GFR), tubular secretion and tubular Re absorption. At the time of birth the GFR is at its lowest this rapidly increasing during the first Two weeks and reaching adult Level.



(https://www.sciencedirect.com/science/article/abs/pii/S1347436718300120)

Fig: *ADME Process*

METHODS FOR ENHANCING PALATABLITY OF PEDIATRIC DOSAGE

FORM:

Many existing medicinal formulations are not design as suitable to children. Therefore, in united state the Best Pharmaceuticals Act for Children and the Pediatric Research Equity Act, and legislation governing the development and authorization of medicines for use in children was also recently introduced. In the European Union to stimulate pediatric formulation development through a combination of market inducement and regulatory requirements. In the pediatric formulation and taste optimization are not well managed then it's difficult to reach the goals. A majority of Formulations for children have complex compositions. In this complex compositions less desirable physical State liquid State, (e.g, liquid state) to provide dose flexibility and facilitate dose administration (e.g., ease-of swallowing). These formulations are more susceptible to taste, physical, chemical,microbiology, and pharmacokinetic issues than those of conventional solid oral dosages for adults .Advanced knowledge in formulation like reaction kinetics, physical chemistry of drug

solubility and forms, and special technologies for taste masking, taste optimization, and bio pharmaceutics is required. A typical development program for pediatric formulations involves:

1]Development Team for the preparations Stage consisting of Formulation and sensory scientist to provide interdisciplinary in put on formulation, composition, and sensory characteristics (e.g. basic tastes, aroma, texture, mouth feel, and aftertaste). This help to clearly define the development strategy.

2.The development Team establishes the viable options in experimental stage.

3. The formulation and establish product, process, and Design space in the optimization Stage.

4. The flavor quality (i.e. palatability) of Formulations (e.g. on age products) verify at the confirmatory stage and conduct stability/ clinical/ bio availability program preparation for product registration. It is important for the project Team to define the strategies to addresses in excipient compatibility,physical and chemical stability,taste, preservative, bioavailability, excipient compatibility, unlikely combinations of accidents can be tested. An approach based on drug substance chemistry, drug/exigent sensory characteristics, exigent properties,and statistical design of experiment recommended generating data and reducing the technical risk. Helps to give the direction for taste-masking and Dosage-forms Selection and Development. The Accidents, including colorants, Sweetener, and flavours for consideration can be based on several acceptance criteria. These factors include regulatory acceptance, toxicity, function such as mouth feel, viscosity and taste; disease state (acute versus chronic, and the Disease itself); administration (dosestrength, volume,and frequency); patient population, market potential dosage form. Example In acute therapy balanced the use of sucrose may be more suitable.

THIN FILM TECHNOLOGY:

The oral thin film (OTF) platform is approve and accepted form of drug delivery for pediatric products. As this Technology emerges as enhancing the palatability of children dosage forms. This technique also provides information about the amount of dose given to children. These dose without water that allows for portable and convenient" give and go" administration by apparent. Patient compliance can be improved Due to an OTF'seas administration and subsequent difficulty in expectoration. These dosage form offers flexibility in base chemistry and base formulation development from raw materials Selection to final packaging configurations as well as an established and well- understood manufacturing path. Based on the continuous nature of production, formulators can also Approach pediatric films, Single product formulations dosage modification of a pre-Existing product.

OTHER METHODS FOR IMPROVING PALATABLITY:

Naturally prepared agent used in this method which are used for improving palatability. These include use of sweetener agents Such as Sucrose and flavoring agents Which enhance palatability The another method which Includes the use of an coatings Such as film coating and sugar coating this method also enhance palatability of poorly palatable drug. Flavoring agent and /or coat drug particles can easily be added to the thin film for the purpose of taste masking. This property enhances the like hood that the infant or young child will continue to suckle the nipple membrane, further ensuring that The Entire dose is consume. In addition, a translucent material can be use for the nipple membrane, so the parent or caregiver can visually determine that the thin film has been completely dissolved and that entire Dose has been administered.

1) Use of sweetener agent:

The use of Sweetener agents not only improve compliance but also attract the children for taking their Daily Dose. Thus children take their medicines easily due to this sweet Taste of drug; this Technique is not harmful because use of naturally occurring Sweetener agents Such as Saccharin and Stevie which is 200 times more sweetener than sugar. Aspartame is known as an artificial sugar which is 150 to 200 time more sweet than sucrose. Sucrose commonly used sweetening agent in formulation as rapidly hydrolyzed in intestine. Mannitol is used as both a diluents and as Sweetener.

2) Film techniques:

This is another method of improvement in palatability of poorly palatable drug in this method the tablet formulated for children will coated with the Thin film of an polymeric membrane .This method also known as an micro encapsulation, In this thin film applied over an tablet which mask it's bitter taste. Another method of Film coating is Sugar coating in which saturated solution of Sugar Applied over tablet and given to pediatric group.

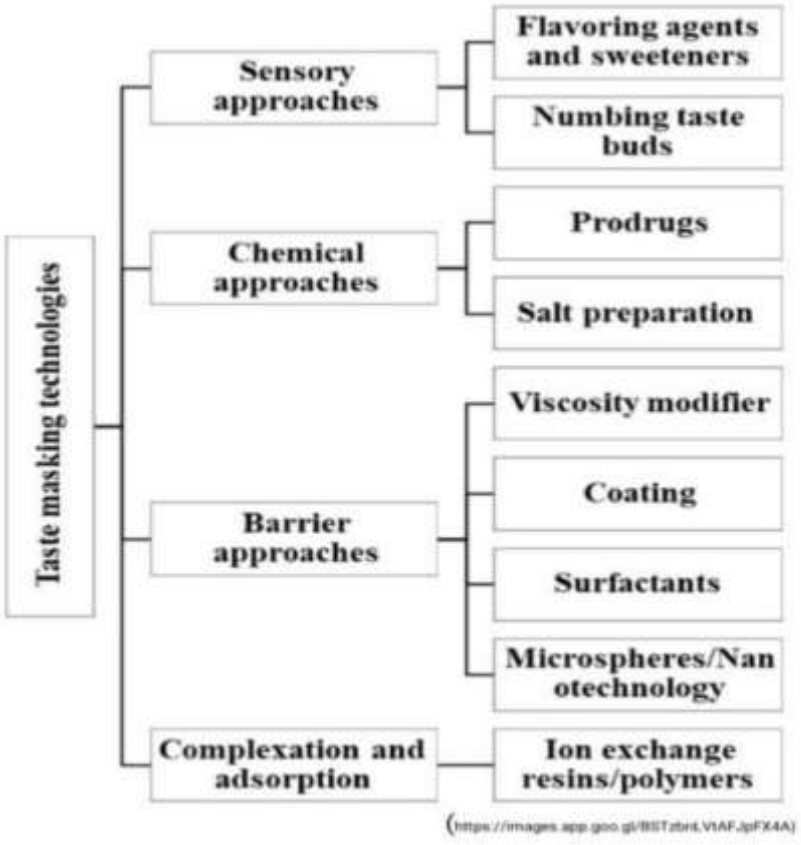


Fig: Taste Masking Agents

3) Colouring Agents:

Pediatric preferred a coloured preparation as they attracted towards it immediately. The Effective colouring agent with a naturally occurring source use as colorants. The majority of colorant uses in oral pharmaceutical formulations four categories:

1)xanthenedyes (quinolineyelow),

2)azodyes (tartazine)

3)Triphenyl methane dyes (erythrosine),and

4)Dyes made from xanthene OR xanthenes derivatives.

4] Ion Exchange Resin Method.

Ion exchange Resins are water insoluble cross-linked polymers containing as salt-forming Group at repeating position so the Polymer chain and have the ability to exchange counter-ions within aqueous Solutions surrounding them. Ion exchanger resins Used in pediatric dosage forms as approach for masking a taste of the drug, for taste masking purpose weak action as well as Weak anion resin are used which based upon the drug Nature.

ADVANTAGES OF IMPROVED PALATABILITY:

PALATABILITY is the most important factor affecting the selection of dose this is due to the taste of drug which we taken is the main factor affecting its usage. Particularly it will relate to the children who are not taking such palatability drug thus it's having following ADVANTAGES which are as:

1] Improved palatability of poorly palatable drug.

2] improved patient compliance.

3] Improved taste of drug.

4] Help in the completion of the drug therapy.

5] Help in maintain the desired Drug concentration in body.

6] Mask the bitter taste of drug.

7] Encourages pediatric patients for taking their medicine.

Precautions During Dosing :

LIQUID DOSAGE FROM	SOLID DOSAGE FORM
For Giving Dosage to Children gives one teaspoon daily or recommended by physician	Tablet not Dissolved in Honey priorror to given to childrens
In case of dosage form is opthalmic don't added directly to children's eye risk of irritation	Tablet not given in large doses
Pediatric medication don't mix with its food risk of interaction	Do not break any tablet formulation

Recommendation During Dosing:

LIQUID DOSAGE FORM	SOLID DOSAGE FORM
Use Measurement systems for giving dose	Encourage parent to teach how to swallow an tablet
Mix liquid in to small amount of water for dilution which makes swallowing easy	Don't break any tablet formulation

RECENTLY APPROVED PEDIATRIC DOSAGE FORMS

(FDA APPROVED)

Pediatric Drug	Disease	Formulation	Year
Ixekizumab	Plaque	Injectable	2020
Crisaborole	Atropic Dermitatis	Ointment	2020
Sofosbuvir	Chronic Hepatatis	Oral tablet	2020
Vilazodone HCL	Depression	Oral tablet	2020
Fidaxomicin	Diarrhea	Oral Tablet	2019
Tazarotene	Acne	Topical	2019
Insulin aspart	Diabetes	Injectable	2019
Ceftarolin Fosamil	Skin infection	Injectable	2019
Minocycline	Acne	Topical	2019
Pitavastatin	Hyperchlorestrolemia	Oral tablet	2019
Cobicistat	HIV 1	Oral tablet	2019
Glucagon	Hypoglycemia	Injectable	2019
Pregabalin	Seizures	Oral solution	2019
Micafungin	Candidiasis	Injectable	2019

Table : Recently Approved Pediatric Dosage Form

CONCLUSION :

This article Focuses on the current aspects of design and development pediatric dosage form and methods to improved its palatability in significant amount so that the pediatric patient takes medication easily without difficulty in swallowing the medication. This Article also focus on the precautions to be taken during giving medication to children's (pediatric patients) thus its an important element to study the pediatric acceptability to type of dosage form, or make medicine more palatable to children's to improve the medication taking behavior of children's.the developments of age appropriate dosage form is difficult task and its also required an consideration and fulfilment of various approaches.The development of new drug formulations for children's

should always consider Palatability in order to avoid future problems in their administration and treatment compliance.There must also considered that even if same illnesses in adult and Pediatric patients but the drug/medicine, dosage frequency in both is different, thus its an important to formulate an age appropriate medicines and with accepted palatability for Pediatric patients is essentially Important.

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