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A REVIEW ON TABLET USAGE AND ITS ACCEPTABILITY IN PEDIATRIC POPULATION

Paediatrics

Beny Margrat C F	Clinical Pharmacist, Department of pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India.
Suwitha S	Clinical Pharmacist, Department of pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India.
Muhammed Nishad P	Clinical Pharmacist, Department of pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India.
Priya A	Executive, Department of pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India.
Arun Chander Yadav K*	Consultant Clinical Pharmacologist, Department of pharmacology, Apollo Children's Hospital, Chennai, Tamil Nadu, India. *Corresponding Author

ABSTRACT

Due to variety of pediatric population and barriers of modern technologies it looks that a single formulation strategy will now not be suited for all pediatric patients. The determination of a suitable formulation strategy for a targeted population crew wants to be cautiously considered for every individual product. When managing patients who can't swallow solid oral dosage forms, switching to choice liquid components or different route is greater suitable. To limit unnecessary drugs manipulation it is fundamental for prescribers to think about age appropriateness, type of formulation (in relation to ease of administration), swallowing issues and patient capability to swallow. Palatability needs to be considered carefully by pharmaceutical companies when designing new formulations and also by prescribers in order to optimize effective prescribing, adherence, therapeutic results and lowering wastage with cost savings. . Majority of drugs prescribed for children have not been competently examined in pediatric population. Future formulation work needs to be carried out to strengthen pediatric based formulations. Formulations accepted by children need to be accessible in suitable unit doses covering child dosing ranges and it should be able to tapered accordingly. Monolithic solid dosage form was discovered to be an alternative choice in case of unavailable liquid dosage form. It is very necessary therefore that all requests to crush, split, or opening of capsules have to be discussed with clinical pharmacist prior to beginning administration of the crushed products.

KEYWORDS

devices, crushing, splitting, palatability, monolithic solid dosage form

1 INTRODUCTION:

Pharmaceutical Formulation is an integral part in developing new medicines. Formulation improvement requires a deep perception on active pharmaceutical ingredient which influences the stability, solubility and bioavailability of the molecule [1]. Drugs are steadily being marketed in an array of sophisticated formulations to enhance the efficacy of the agent [2]. Patient acceptability is crucial to maximize patient adherence in order to attain efficacy and safety of medicines. Prescribing well accepted formulations is one of the upmost essential parameters to be followed in pediatric population.

Due to variety of pediatric population and barriers of modern technologies it looks that a single formulation strategy will now not be suited for all pediatric patients. The determination of a suitable formulation strategy for a targeted population crew wants to be cautiously considered for every individual product [3].

Oral route of drug administration is the most popular and effectively used route for conventional delivery of drug. Solid oral dosage types such as capsules and tablets are the most frequent administration on oral routes. Unfortunately, many people struggle to swallow solid oral dosage forms whole so alternatively cutting, crushing or opening tablets are done to make them simpler to swallow [4]. When managing patients who can't swallow solid oral dosage forms, switching to choice liquid components or different route is greater suitable [5]. Liquid dosage types may additionally be greater favorable for patients such as neonates and toddlers due to the increased dose flexibility and ease of swallowing in contrast to solid oral dosage forms [3].

In younger children and patients with distinctive conditions (presence of a feeding tube) it is tough to take tablets formulations as whole tablets or capsules even after crushing [6,7,8]. The manipulation of medicinal products to extract a section of the total dosage form, in facilitating administration becomes a frequent practice in pediatric drug therapy.

The term manipulation consists of splitting, crushing or suspending in case of tablets and Opening or suspending the content material in liquid if it is capsule. These steps are not often supported through the manufacturer's products summary or other guidelines. But this manipulation is made ordinarily to enhance acceptability of medicines [9,10,11,12,13].

1.1 Tablets:

Tablets are defined as solid pharmaceutical oral dosage forms containing medicament with or without suitable excipients. Tablets are made by compressing one or more substances using a tablet press or via molding [14]. There are different types of tablets available in the market. Tablets are the first preference in choosing a pharmaceutical dosage form for a patient. Which have greater advantages over all other dosage forms. Tablets have the best blended properties of chemical and microbiological stability amongst all other dosage forms [15].

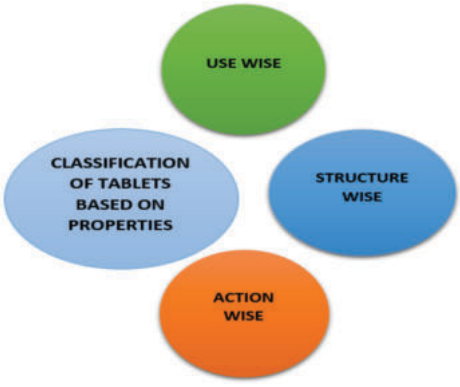

Figure: 1 Classification Of Tablets Based On Properties

- Tablets for oral ingestion
- In oral cavity
- By other routes
- To prepare solution
- Divisible tablets
- Aperture tablet
- Concave convex tablet
- Core tablet
- Layered and in layered tablet

Modified release tablets
- Timed release
- Sustained release
- Prolonged release

Delayed action tablet
- Enteric coated
- Rapidly dissolving / Disintegrating tablet

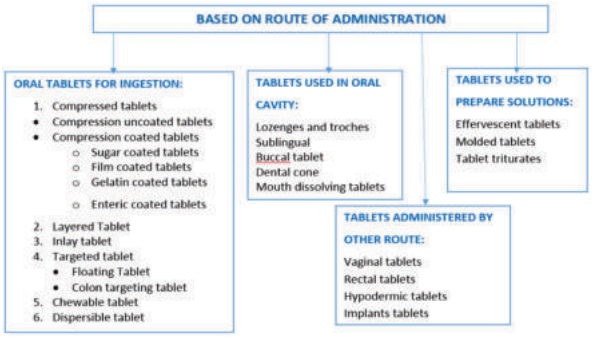

Figure: 2

Age Appropriate Acceptability:

Acceptability problems show up to be frequently due to the shortage of child-friendly dosage forms available at the market. Even though there are tremendous formulations accessible in market. Pediatric based formulations are observed to be minimal. So Palatability of oral medication determined to be essential in pediatrics with all other formulations [16]. Acceptability is described as the overall ability and willingness of the patient to use and its care giver to administer the medicines as prescribed. Acceptability has emerged as a key component for treatment effectiveness as it might negatively influence patient adherence. "Acceptability and preference amongst distinctive paediatric dosage types are known to differ between children. Parameters such as Child's age, individual health status, behavior, disabilities, heritage and lifestyle should be viewed in determining the child's acceptability and preference."

"The dimension and structure of a tablet are also essential in case of acceptability & ability of child to swallow it. The acceptability of the size and shape of tablets by the target age group(s) should be justified. It has been established that making medications more pleasing to the child can have a positive impact on compliance [15].

Palatability desires to be viewed cautiously via pharmaceutical companies when designing new formulations and by prescribers in order to optimize effective prescribing, adherence, therapeutic outcomes and lowering wastage with cost savings. So acceptability plays an integral role in medication adherence [17].

Splitting And Crushing Of Tablets:

The negative impact of usage of oral tablets in pediatrics is difficulty or inability in swallowing experienced by younger children. Tablets could be considered as accepted in children 6 years and older, that seemed no longer to be the case amongst younger children as expected [16]. In the absence of alternative age suitable dosage forms, different techniques for administering oral solid preparations are considered through applicants. These Dose adjustment are frequently accomplished through tablet splitting, crushing or grinding. Tablet splitting can be advisable while tapering or titrating medication regimens by eliminating the need for a separate prescription for higher and lower doses [18,42]. Tablets are often split by patients on oral drug therapy [19]. Some health care systems and managed care companies have adopted tablet-splitting programs [20]. Most guidelines advise using a mortar and pestle or a tablet crusher [21].

Figure 3

Tablet splitting refers to the practice of dividing a tablet into two pieces. Crushing of tablet is pressing it very hard to break its structure to a powder form. Patients in all age groups can use tablet form via splitting or crushing them when necessary.

People do this for multiple reasons:
- The dimension of the tablet makes it too tough to swallow.
- The right dose of a medicinal drug is not available from the pharmacy.
- Splitting one greater strength tablet into two lower strength pills
- Decreasing drug related costs
- For administration with the aid of enteral tubes [22].

Figure 4

There are wide range of reasons for splitting and crushing but the supreme reason is for people who cannot swallow tablets and patient on enteric tubes. There is no harm in the usage of uncoated or film/sugar coated tablets which do not have change in pharmacokinetic effectiveness, by means of breaking-splitting them. But if the tablet exhibit sustained-release or enteric-coated properties crush only under the recommendation of healthcare professionals or clinical pharmacists [23].

Reason Behind Why Should Not Crush/split:

Any modification of the preparation will change the pharmaceutical characteristic of the preparation as justified via clinical trials and (bio) pharmaceutical studies.

1. Crushing, dispersing or splitting impose a direct exposure to the pharmaceutical ingredient which may also generate palatability issues. Common tablets which relates to this are methotrexate, tamoxifen, finasteride, preparations containing hormones such as hormonal replacement therapy and corticosteroids, e.g. dexa methasone.
2. Some drugs are toxic when inhale but the exact reason is unknown. Several drug substances might cause inflammation if the powder comes into contact with the eyes, skin, or other mucous membranes e.g. Alendronate.
3. Some drugs might cause irritation to the stomach or esophagus if the formulation is changed, e.g. nitrofurantoin, diclofenac and aspirin.
4. Many tablets have a bitter taste or often distaste. Crushing, opening or splitting medication may also make it unpleasant for the resident to take and this might also cause them to refuse their medication. Common tablets with bitter / unpleasant taste are quinine, ciprofloxacin, cefuroxime, quetiapine and ibuprofen.
5. Drugs can also have an anesthetic impact on the tongue, e.g. sertraline [24].
6. Crushed tablets were given whole with meals or drinks to enhance palatability. Beyond dosage form manipulation, mixing with meals or drink may alter the biopharmaceutical traits and product's usual performance. Due to children's variations in meals consumption and body composition, food-drug interactions can't be envisioned primarily based on adult studies [24,41].

Tablets That Should Not Be Crushed

There are certain tablets that are designed to be dispersed in certain parts of the body or at a specific rate. Crushing certain drugs can cause them to be released too early or too rapidly and will increase the risk of side effects. It additionally reduces the absorption and effectiveness of the drug. Some of the tablets which should not be crushed includes,

Sublingual and buccal tablets:

These tablets are designed to dissolve in the oral fluids of the mouth for rapid and complete absorption than is possible in the stomach. Many of these medicinal drugs are destroyed by the gastric juices in the stomach. Crushing this kind of tablet can have an effect on the pharmacokinetic of the drug.

Opioid drugs:
They are designed to be released at a controlled, constant rate to avoid an unintended "high" and feelings of euphoria that promote addiction.

Enteric Coated Tablets:
Also known as gastro resistant tablets these tablets are designed to get dissolved in intestinal tract. Chewing or crushing may leads to destruction of medicine via stomach acids. Prolonged action of medicinal drugs cannot be achieved and also may results in irritation of the lining of stomach [24].

Modified release medicines:
It can be recognized by using the letters such as M/R, LA, SA, CR, XL or SR at the end of the name. Words such as "Retard", "Slow" or "Continues" in the title is occasionally used instead. These tablets are designed to get released over an extended period, this mechanism can be damaged if the drug is manipulated.

Film or sugar-coated medicines:
These drugs are designed to masks its unpleasant taste Disruption of the film or sugar coating on a drug may additionally result in rapid degradation of the active ingredient. Crushing these tablets consequently may not critically affect how the drug is released but may cause the resultant combination to be unpleasant to taste which is likely to affect patient adherence [25].

Coated and Uncoated tablets:
Avoid crushing of tablets in patients with dysphagia or a feeding tube [26,39].

Crushing Devices:
The European medicines agency (EMA) Pediatric Committee's (PDCO's) Formulation Working Group (FWG), recommend that a suitable and dispensing device need to be available to enable size of the required doses and to count multi particulates [17]. In the latest study, it is reported that the usage of a tablet splitter is greater successful than splitting by hands and cutting devices such as scissors or a knife [27]. Electronic devices are also available, which function on the same concepts however have a button- activated crush to reduce user fatigue.

There are two major kinds of manual tablet crushers,
- Crusher one includes lifting a lever up and down to exert a crushing stress on the crushing pad
- Tablet crusher which performs a twisting action i.e. inserting a crushing member into a container for a rotating or grinding motion to crush the tablet inside the container [28].

There are three main types of devices:
- Pill crusher: Most tablet crushers are hand held devices twist to grind a tablet into fine powder. Others seem like a stapler or garlic press that grip to crush the pill.
- Mortar and pestle: A mortar and pestle is an instrument used for pounding and breaking material. It is used to grind tablet manually.
- Pill splitter: This hand held device helps to cut tablet into halves or quarters so that they can easily swallow [22].

Disadvantages Of Splitting
- Several publications revealed that dose accuracy and weight uniformity are particularly based on the manipulation technique used [27].
- Bioavailability and pharmacokinetic facts are missed for manipulated dosage forms [28].
- Splitting or crushing these medicines can have deleterious effects on pharmacokinetic properties.
- Stability of the dosage form is the responsibility of the manufacturer; however, if the drug is altered out of medication administration guidelines, the clinician may additionally held accountable [29].
- The accuracy of tablet splitting can be affected based on tablet shape, size and technique/ device used [30].
- A variety of drugs will be potentially poisonous to the person crushing or administering tablets, via inhalation of the powder.
- There is always the risk of sensitization or anaphylaxis in susceptible individuals.
- If the device used for crushing is not properly cleaned, the potential to contaminate different preparations can occur [31].
- Blockage of tube can happen when administered through enteral feeding tube due to particle size, viscosity and chemical compatibility of oral medicinal products when interacted with tube material.
- Mixing with meals or drink is used to masks the unsatisfactory taste and palatability of formulation but this can affect the product overall performance and pharmacokinetic behavior [16].
- Prolonging the contact time of a drug with a foodstuff is likely to extend the binding capability and reduces drug bioavailability which can alter the therapeutic response [32].
- If a drug-foodstuff combination is not consumed entirely, the desired dose will not be reached properly as prescribed.
- Excipient forms the main bulk of almost all dosage forms. Although excipients are essentially non-hazardous. Only limited information are available on the acceptability and safety of formulation excipients in relation to the age and development status of the child [2].

Barriers To Oral Medicines Administration
- Taste was the most often reported barrier
- Volume or Quantity
- Size, distaste & issue with swallowing
- Color
- appearance and odor
- Food drug interaction
- Onset of action is slow

Recommendations During Crushing:
- Separate the tablet crusher parts if viable
- Wash every part with warm running water and a mild dishwashing soap to get rid of all medication residue.
- Allow airing dry or wipe with a lint free towel.
- Glove use is recommended to protect the child and care giver.
- Use Alternative medicines/formulations/routes if accessible as an alternative of crushing.
- Assess swallowing capability before crushing.
- Patient monitoring must be undertaken when some products are crushed.
- Discuss with clinical pharmacist earlier before crushing due to the fact that crushing certain products might produce modifications in the drug pharmacokinetics and bioavailability resulting in under dosing or adverse effects.
- Crushing an oral solid dosage form can also have a poor impact on the stability of the drug Substance. So crush medicines prior to administration.
- Medication crushing need to be carried out in a clean contaminated place preventing indoor air pollution area [33,40].

Practical Aspects Of Administration:
- Medications should not be added directly to nutritional formulations.
- If capsules can be opened then they have to be opened and blended with 10 to 15ml of sterile water.
- The tube have to be flushed with 30ml of sterile water prior to administration of the drug if administration is via enteral tubes.
- The medicinal drug need to be blended straight away prior to administration.
- When more than one medicinal drugs are administered 5ml of sterile water have to be flushed between tablets to avoid drug interactions.
- If the medicine is meant for administration in the cheek or beneath the tongue it must be continued to use with the aid of those routes. Crushed products via enteral tubes may get clogged so flushing should be done appropriately.
- If a couple of medicines wants to be administered, administer one medicine at a time.
- Allow tablets to get disperse completely [24].
- Give the complete medicinal drug dose totally even if it is mixed with feeds.
- Discuss with health care professional or clinical pharmacists before mixing crushed medicines with foods.

DISCUSSION:
It has been established that making medicines greater pleasing to the child can have a positive impact on compliance. To limit unnecessary drugs manipulation it is fundamental for prescribers to think about age appropriateness, type of formulation (in relation to ease of administration), swallowing issues and patient capability to swallow tablets in accordance to dimension and textures of tablets [30].

Bioavailability and pharmacokinetic information for manipulated dosage forms found to be unavailable [28]. Most guidelines advise the use of mortar and pestle or a tablet crusher [21]. In the latest study, it is suggested that the use of a tablet splitter is greater successful than splitting through hand and cutting device such as scissors or a knife [27]. Crushing products with carcinogenic potential can also expose care givers or healthcare professionals via powder aerosolisation and such should not be undertaken [33]. The impact of mixing the product with common meals or drinks need to be discussed for each and every oral pediatric medicinal product with health practitioner or clinical pharmacist [24].

Clinicians and consumers get necessary facts about appropriate use of drugs and related risks from the product label which is derived from controlled clinical studies. However, restricted variety of tablets are examined in pediatric patients, the product label lacks unique information for many drugs used to treat children. This scenario creates challenges for clinicians who deal with children of complete pediatric range, i.e., toddler to adolescent and this leaves clinician and end consumer to use the available adult formulation in the market for pediatric population [2]. If the major motive of breaking and splitting of drugs is to deal with the patient with a lower dose, the accuracy of breaking-splitting is very important. If a pill is FDA-approved to be split [35]. It is safer to break up via the break marks provided in the tablets. Patients often follow the techniques such as dividing doses, crushing and dissolving them in liquids (water, juices, etc.), and administering them in portions that have no longer been properly tested. In this respect Albertini et al. investigated the compatibility of solid lipid micro particles in milk and yogurt as appropriate vehicles for pediatric administration [36].

Milk has been explored as a vehicle in liquid formulations showing potential for solubilizing drugs while maintaining the stability of the emulsified vehicle [37,38]. In addition, the co-administration of drug products with meals or drinks causes safety concerns, such as over dose or under dose consumption and have an effect on drug's bioavailability [39]. Limited evidence is available on the consequences of mixing tablets with quite number of foodstuffs. Even though some Studies recommend combining tablets in vehicles there are incomplete reviews on mixing pills with food [32]. A new improvement is made for overcoming dysphagia by means of using oral swallowing gels to swallow whole, crushed, or pulverised tablets [43].

Palatability needs to be considered carefully by pharmaceutical companies when designing new formulations and also by prescribers in order to optimize effective prescribing, adherence, therapeutic results and lowering wastage with cost savings [17]. Few research reports that solid dosage forms that are small in measurement (2–3 mm), recognized as mini tablets may additionally be accepted by means of children from birth [16]. But further investigations are needed.

The technique of conduct and design aspects of these pediatric trials, have extended due to the increasing involvement of pediatric expertise. The validated biomarkers that could be used for pediatric population are limited in number. Therefore, application of the accessible adult biomarkers are directly used to collect pediatric information. Majority of drugs prescribed for children have not been competently examined in pediatric population, especially with younger age group, as much fewer data is available, to conduct the pediatric study. Any change of the preparation will change the pharmaceutical traits of the preparation as justified via the scientific trials and biopharmaceutical studies [2].

CONCLUSION:

This article provides facts about the challenges faced throughout selection, administration and acceptability of drugs in pediatric population. Although understanding and awareness on acceptability problems has been accelerated amongst healthcare professionals. Further research need to be done to develop age-appropriate formulations and acceptability. Age-appropriate formulations are the supreme conclusion for the above discussed drawbacks. Future formulation work needs to be carried out to strengthen pediatric based formulations. Formulations accepted by children need to be accessible in suitable unit doses covering child dosing ranges and it should be able to tapered accordingly. Monolithic solid dosage form was discovered to be an alternative choice in case of unavailable liquid dosage form. Physician have to prescribe different dosage formulations such as liquid formulations if available. Which has been accepted by children's. Physicians and clinical pharmacists must constantly discuss the appropriateness of possible alternatives thinking about both the characteristics of drug and patient acceptability. It is very necessary therefore that all requests to crush, split, or opening of capsules have to be discussed with clinical pharmacist prior to beginning administration of the crushed products.

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