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# CHALLENGES IN PEDIATRIC FORMULATIONS DEVELOPMENT: A REVIEW

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## ABSTRACT

Drug formulations used in pediatric pharmacotherapy should be adapted to children's needs to suit their age, size, physiologic condition, and treatment requirements. Such pediatric medicines are keys to achieving safe and accurate dose administration, reducing the risk of medication errors, enhancing medication adherence, and improving therapeutic outcomes in children. The use of inadequate drug formulations in children may pose problems not seen in adults, such as difficulty in swallowing, safety issues with certain excipients that are acceptable in adult formulations and adherence problems with unpalatable medicines. Only a small fraction of all marketed drugs are available in formulations that are age appropriate and suitable for pediatric use. As a result, many adult medicines are used off-label in children, a practice that carries additional health and environmental risks. A number of innovative pediatric formulations have followed, but their actual effect on pediatric drug approvals remains to be seen, as clinical trials and marketing authorization take a substantial amount of time. To optimize pharmacotherapy in children, it is important for clinicians to understand the background of the aforementioned problems as well as to gain insight into the challenges, developments, and potential solutions. The aim of the present study was to describe specific challenges for pediatric drug formulations and to address the absence of adequate availability palatable formulations for children. We will discuss the major challenges in pediatric formulation and development, role of acceptable palatability in achieving adherence of pediatric population for pharmacotherapy and getting maximum outputs, the necessity of pediatric formulations and future steps.

**KEY WORDS**: Pediatric Formulations, Challenges in Pediatric formulations.

## INTRODUCTION

Children represent a vulnerable group, with parental consent for treatment relying on the evidence-base and expertise drawn upon by professionals caring for them. Before any medicine is authorized for use in adults, the product must have undergone clinical testing to ensure that it is safe, of high quality and effective. This is not the case with all medicines for hospitalized children as, depending on speciality, between 30 and 90% are not licensed for purpose (termed "off label" OL) or have not been licensed at all (termed "unlicensed", UL). This is also the case in the community but possibly to a lesser extent.

Using medicines that are not licensed means there is limited available evidence on safety, quality and efficacy and a potentially increased risk of adverse drug reaction. In addition to a lack of systematically compiled evidence for the use of unlicensed medicines, many are available only as solid dosage forms. Depending on age many children are unable to swallow whole tablets or capsules even when given specific training. Furthermore, as dosing is often based on body weight, only a proportion of a solid dosage form has to be given which can be difficult to achieve.

A 'paediatric drug formulation' as a dosage form which is suitable for accurately, safely, effectively, and adherently administering a medication to children of various ages. The World Health Organization (WHO) approximates that more than 50% of medicines prescribed for children, including many of those on the Model List of Essential Medicines for Children, do not actually exist in dosage forms appropriate for children. Even when pediatric formulations exist, clinical availability varies. Consequently, health workers often dispense adult dosage forms with instructions on how to achieve desired pediatric doses. This may include instructing caregivers to break tablets, crush pills, open capsules and estimate dose, or use medicines formulated for intravenous injection as oral liquids. Use of medicines in such a manner can lead to inaccurate dosing and result in potentially reduced efficacy (due to under-dosing) and/or adverse effects (due to excessive doses.) Formulations of drugs are fundamentally important because they help to determine whether the dose will be successfully delivered to paediatric patients; however, information on how best to prepare and administer paediatric drug formulations in any cultural setting is often lacking. This is a critical global health issue.[1]

Children differ from adults in many aspects of pharmacotherapy, including capabilities for drug administration, medicine-related toxicity, and taste preferences. It is essential that

pediatric medicines are formulated to best suit a child's age, size, physiologic condition, and treatment requirements. To ensure adequate treatment of all children, different routes of administration, dosage forms, and strengths may be required. Many existing formulations are not suitable for children, which often leads to off-label and unlicensed use of adult medicines. New regulations, additional funding opportunities, and innovative collaborative research initiatives have resulted in some recent progress in the development of pediatric formulations. These advances include a paradigm shift toward oral solid formulations and a focus on novel preparations, including flexible, dispersible, and multi-particulate oral solid dosage forms. Such developments have enabled greater dose flexibility, easier administration, and better acceptance of drug formulations in children. However, new pediatric formulations address only a small part of all therapeutic needs in children; moreover, they are not always available. Five key issues need to be addressed to stimulate the further development of better medicines for children:

**1. Unmet formulation needs for pediatric patients, particularly drug delivery in neonates and treatment gaps in pediatric and childhood diseases**[2]

Using medicines that are not licensed means there is limited available evidence on safety, quality and efficacy and a potentially increased risk of adverse drug reaction. In addition to a lack of systematically compiled evidence for the use of unlicensed medicines, many are available only as solid dosage forms. Depending on age many children are unable to swallow whole tablets or capsules even when given specific training. Furthermore, as dosing is often based on body weight, only a proportion of a solid dosage form has to be given which can be difficult to achieve.

Acceptable palatability is paramount for paediatric formulations. Palatability is largely dictated by taste and this is a concern as a significant number of active pharmaceutical ingredients (APIs) on the market and in development have aversive taste. This is not considered to be a key issue when developing oral dose forms for adults who can swallow tablets since such products can be film or sugar-coated, thereby masking the taste of the API. In the paediatric population the issue is accentuated by dysphagia, leading to an increased use of oral dosage forms such as liquids, (oro-) dispersible and chewable tablets where taste masking becomes a greater challenge. In addition, differences in taste perception, sensitivity and tolerance between adults and children make taste assessment and development of palatable paediatric medications more complex.

The paediatric population represents a diverse group of patients, exhibiting differences in biological and physiological attributes compared to adults. Indeed, children are not merely miniature adults because sensory systems mature post natally and their responses to certain tastes differ markedly from adults. Amongst these differences are heightened preferences for sweet-tasting and greater rejection of bitter-tasting foods. In addition, APIs and excipients are metabolized differently by children of different ages compared to adults. Therefore the use of certain Excipients may not be appropriate or the levels will be restricted, which further complicates excipients selection. Indeed, when designing an age-appropriate paediatric medicinal product, the excipients used should be selected using a benefit risk approach.[3-4]

**(2) Limited data availability**

Peadiatric formulation development and clinical data availability is limited. If available, it is scattered. Hence, for betterment of pediatric formulation and development it is necessary to collect the data available. Children are particularly vulnerable to medication dosing errors because of the unique circumstances involved in prescribing medication to children. In the ambulatory setting, several factors likely contribute to medication errors include the following:

1. Accurate weight must be obtained and correctly transcribed;
2. Health care provider may need to convert pounds to kilograms;
3. Health care provider must make rapid weight-based calculations for nearly every pediatric prescription he or she writes;
4. Correct preparation and concentration (liquid, chewables, tablets) of the medicine must be included in the dosage calculation;
5. Total daily dose may need to be divided into multiple doses to obtain the appropriate frequency for the medication;
6. Communication with the parent or caregiver often will occur without the medication present;
7. Prescription must be legible and correctly interpreted by the pharmacist; and
8. Pharmacist must dispense the appropriate medication in its appropriate formulation labeled with the appropriate dose and frequency.

Furthermore, children cannot always communicate symptoms that may alert parents and providers to an adverse drug reaction if a medication overdose or underdose is taken by the patient. Many subtleties and challenges may arise during the course of our studies:

1. Off-label use of medication in children is common, particularly for psychotropic medications and other newer classes of medications. Many times, pediatric doses for these medications are difficult to find and may be extrapolated from adult doses with little scientific evidence to support safety and efficacy.
2. Published sources of pediatric dosing information differ in their recommendations for dosing ranges for children, sometimes by as much as a two-fold difference in the maximum recommended dose. Furthermore, ranges provided for weight-based dosing often encompass large ranges, sometimes as much as four-fold differences between the minimum recommended dose and the maximum recommended dose.
3. Indications for appropriate adult dosing is in total milligrams per day (mg/day) rather than in weight-based milligrams per kilogram per day (mg/kg/day), the system for indicating dosing for children.
4. Determining medication errors in children is only possible with accurately documented weight in kilograms.[5]

**(3) Evaluation challenges of Novel approaches in pediatric formulations**

Acceptability is an overall ability of the patient and caregiver (defined as ‘user’) to use a medicinal product as intended (or authorized). Acceptability of a medicinal product is likely to have a significant impact on the patient's adherence and consequently on the safety and efficacy of the product. Acceptability is driven by the characteristics of the user (age, ability, disease type and state) and by the characteristics of a medicinal product such as:

- Palatability
- Swallowability (volume/size and shape, integrity of dosage form, e.g. Functional coating)
- Required dose e.g. The dosing volume, number of tablets etc.
- Required dosing frequency and duration treatment
- Selected administration device
- Primary and secondary container closure system
- Actual mode of administration.

The majority of API's have an unpleasant taste. The pragmatic approach often taken by patients and carers to facilitate dosing is to dilute or obscure the taste of a medicinal product

by mixing or sprinkling it in food/beverages. However, there are risks associated with using this approach. For example the entire dose of the medicinal product may not be consumed especially if the volume or quantity of food/ beverage is too large or taste not appropriately masked. In addition, this approach may result in the child being put off the food/beverage used, which could be a particular issue for very young children and babies where milk is the main food source. Hence mixing with food or beverage should not be the primary means of taste masking a formulation. Orodispersible dosage forms are those that disintegrate or dissolve rapidly in the oral cavity, resulting in a solution or suspension without the need for water. In terms of specific use for pediatric and geriatric population groups, their primary advantage is their ability to be administered to those with difficulties swallowing solid dosage forms. However, disadvantages include limited drug loading and the requirement for taste masking.

During development formulator usually has no or very little information about taste of the formulation. It is therefore difficult to assess whether taste of the formulation has been masked. This emphasizes the need to generate taste data at an early stage during the development programme, to direct pediatric formulation development. However, as the available in vitro methods, like electronic tongue, for taste prediction are currently limited, the only way to reliably assess palatability of formulations is a taste study in humans. The perception of taste of medicines has been shown to be different between adults and children and will probably differ between healthy and sick children. Thus, ideally taste should be assessed in children, but there may be some ethical concerns to perform taste studies in healthy children unless the study is a 'swill and spit' one with drugs known to have a good safety profile. The EU ad hoc committee considering ethical aspects of clinical trials in children has stated: 'In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable like children with a disease or condition. Studies should not be performed in children when they can be performed in adults. Exceptions could be where healthy children participate in palatability testing such as swill and spit taste testing for a new flavoured medicine' (EMEA, 2008). For many drugs, e.g. cytotoxics, it would be considered unethical to enroll healthy volunteers, even in 'swill and spit' tests. These should have taste assessed when administered to children with the illness to be treated and the study should preferably be imbedded within another clinical study. An advantage is that taste can be assessed during multiple dosing where results may differ from single administration studies in volunteers. Informed consent to taste studies must be

obtained from the person with legal responsibility for the child and assent of the child should be obtained wherever possible. Carrying out taste tests in.

Children are associated with a variety of practical and technical challenges, including questionnaire design and reliability of paediatric responses. Interpretation of study results can be difficult as well, as a standard definition of 'acceptable taste' does not exist. Whilst it is important that the taste of the formulation does not impact compliance, the scenario of a 'too pleasant', 'candy-like' formulation with its potential risks (e.g. overdosing and poisoning) also needs to be considered.[6]

**(4) Availability of clinical data and evidence of the impact of novel formulations**

Enrollment of children into pediatric clinical trials remains challenging. More effective strategies to improve recruitment of children into trials are needed. In-depth qualitative interviews with parents who were approached to enroll their children in a clinical trial have thrown light on the barriers to pediatric clinical trial participation.

In general, enrollment of children into clinical trials is challenging because of the relatively small number of available participants, ethical concerns regarding participation of children in trials, and technical challenges such as blood volume collection limitations and monitoring required for certain trials. These factors are further complicated by the challenges of obtaining parental consent for the child to participate. Studies have shown that parental willingness to allow their children to participate in clinical trials is variable based on numerous factors, including: recruitment strategies used, age of the child, race, socioeconomic status, type of study or the perceived risk, and health status of the child. Fewer data exist that describe specific operational tactics and interventions that have the most impact on parents' perceptions of clinical trials. Establishing trust, appropriate timing, a transparent discussion of risks and benefits oriented to the layperson, and providing motivation for children to participate were key factors that impacted parents' decisions. Fewer data exist that describe specific operational tactics and interventions that have the most impact on parents' perceptions of clinical trials.

In order for clinical trial accrual to be successful, parents' priorities and considerations must be a central focus, beginning with initial trial design. The recommendations from the parents who participated in this study can be used to support budget allocations that ensure adequate training of study staff and improved staffing on nights and weekends. Studies of parent

responses in outpatient settings and additional inpatient settings will provide valuable information on the consent process from the child's and parent's perspectives. Further studies are needed to explore whether implementation of such strategies will result in improved recruitment for pediatric clinical trials.[6-7]

**(5) Improved access to new pediatric formulations**

Alack of appropriately authorized medicines for the pediatric population is a major problem as it often leads to inadequate treatment of children. This problem is global and universally affects children in developing and developed countries.

One of the limiting factors for access to medicines in the pediatric population is the availability of oral formulations that are suitable for children. A study conducted in Serbia, the USA, and Germany showed that significant country-to-country differences continue to exist in both of the number and type of oral drug formulation that have pediatric labeling. Since neonates and young children are not able to swallow tablets and capsules, lack of suitable oral formulations' medicines has major consequences. One of the consequences is preparation of medicines extemporaneously in local pharmacies. This kind of children's treatment is considered as unacceptable because efficacy and safety of these products has never been evaluated. Furthermore, intravenous drugs are often too concentrated and therefore not suitable for the neonates and young children use without modification.

A broader approach should be used to better describe the total availability of pediatric formulations worldwide. In addition to licensing and labeling, the cost of the medicines and reimbursement by health insurance coverage also determine accessibility.

Although great progress has been made over the past few decades in resolving some ethical, technological, and scientific problems in pediatric pharmacology, little success has been seen in improving the availability of medicine for children.

Pioneering legislation on pediatric medicines came into force in the United States in 1997. In 2007, European Union's Paediatric Regulation was adopted with the aim to promote the development and improve the availability of medicines for children of all ages, ensure high quality of medicines, and provide the information about the safety, effectiveness, and dosage of drugs for the pediatric population.

In the same year, the World Health Organization (WHO) published the first "Model List of Essential Medicines for Children" and started the campaign "Make Medicines Child Size" to raise awareness about the global problem affecting pediatric therapy. With the relatively recent implementation of these initiatives, we do not immediately expect a complete resolution of the problem of "therapeutic orphans," yet we believe that enough time has passed for initial concrete results.

Significant differences in the availability of drugs suitable for children exist worldwide. From global health point of view, the differences in the access to children formulations should, therefore, be of the highest priority. Several World Health Organization (WHO) initiatives aim to improve the accessibility of safe and effective medicines for children. A first step in achieving this goal is to obtain a baseline measure of access to essential medicines.

Analysis of the procurement, supply and distribution of specific medicines is needed to determine reasons for lack of availability. Improvements to accessibility could be made by developing an essential medicines list for children and including these medicines in national purchasing lists.[7-10]

**Necessity of Pediatric Formulations**

It has been well established that children are not small adults but rather a distinct and heterogeneous patient group with regard to pharmacotherapy. They often exhibit a different response to both active substance and Excipients. Children present a continuum of growth and developmental phases as a result of their rapid growth, maturation of the body composition and physiologic and cognitive changes during childhood. Children differ from adults in many aspects of pharmacokinetics and pharmacodynamics, potential routes of administration, medicine-related toxicity, and taste preferences. Important pharmacokinetic differences between children and adults include the rate of gastric emptying and pH, gastrointestinal permeability and the surface area available for drug absorption.

Dissimilarities have also been reported in drug metabolism, transporter expression, biliary function, and renal clearance, resulting in differences in drug disposition and elimination. The largest deviation from adult pharmacokinetics is observed in the first 12 to 18 months, when organ functions are developing. In older children and adolescents, the pharmacokinetic parameters approach adult values and are thus easier to predict. The effect of age on pharmacokinetics leads to different dosing requirements for different age groups. From birth

to adulthood, the body size and weight of an average child increases up to 20-fold, and the magnitude of dose variation administered throughout childhood may be 100-fold. More dramatically, premature neonates admitted to the hospital can weigh as little as 500 g, further highlighting the need for dose variability. Maturation processes in children are not linear, and therefore doses in certain age subsets may be lower, identical to, or higher than in adults, depending on a drug's metabolic pathway. Due to this extensive variability in children, there is an obvious need for drug formulations tailored to children in all the target age groups. The International Conference of Harmonisation divides childhood into 5 age groups related to the developmental stages, derived from the physiologic and pharmacokinetic differences mentioned earlier. These groups (with age ranges) are:

1. Preterm newborn infants;
2. Term newborn infants (0–27 days);
3. Infants and toddlers (1–23 months);
4. Children (2–11 years); and
5. Adolescents (12–16 years in the United States or 12–18 years in the Europe).

The European Committee for Medicinal Products for Human Use further subdivides the age group "children" (2–11 years) into "preschool children" (2–5 years), and "school children" (6–11 years) to more precisely reflect the children's ability to accept and use different dosage forms. However, the classification of the pediatric population into age categories is to some extent arbitrary because children of the same chronologic age may still develop at different rates. Age-Related adherence to pediatric drug formulations, formulation acceptability and preferences facilitate medication adherence in children and these are important factors in achieving the intended treatment outcomes. Formulation acceptability differs across age groups as children gradually develop their cognitive and motor skills and improve their ability to swallow medications. At certain ages, the dependence on caregivers also plays a role in the administration of pediatric dosage forms. Pain, discomfort, and an unnecessary burden on children and/or caregivers during drug administration should be minimized to assure adequate medication adherence. Taste attribute is critical to ensure acceptable adherence to pediatric oral formulations. Because children have a low tolerance for disagreeable taste, the use of tasteless or palatable medicines can minimize the loss of medication from spillage and/or spitting. Taste preferences may differ between children and adults, as children prefer sweet flavours and dislike bitter taste. These findings suggest that taste assessment should involve children early in the drug formulation development.

Children's communication about taste perceptions can be facilitated by using age-appropriate methods, scales, and measures. Alternative taste-screening methods may include adult taste panels with validated design for data transferability or predictive electrochemical sensor systems (so called "electronic tongues").[11-16]

## CONCLUSION

Scarcity of research within paediatric area and lack of details of the dose (age related dose) of paediatric medicines are important pre-requisites in design of any paediatric formulation. Children often prescribed medicines that are off label, unlicensed or that have been manipulated prior to administration. As a direct consequence, children and their care givers do not have access to safe, effective and appropriate medicine and dosage form. Historically, the failure to appreciate the developmental changes in children has led to many adverse outcomes in clinical practice. Use of medicines in pediatric drug development is associated with numerous challenges, including methodological and ethical requirements for pediatric trials, high developmental costs, and a small and fragmented market. As a result of these challenges, there have only been limited research efforts to adapt medicines according to pediatric needs. Thus the pediatric market has focused mostly on only a limited number of therapeutic areas, such as anti-infectives, hormones and medicines for the respiratory and central nervous system, even authorized pediatric medicines may not always be age appropriate with respect to dosing, suitability of dosage forms, and excipients. This lack of pediatric formulations often leaves health care professionals no alternative but to use adult medicines in an off-label or unlicensed manner.

It is a challenge to find one formulation appropriate for all age groups. The aim should be to safely cover as wide an age range as possible with a single formulation. There is limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs. The administered dose should contain an amount of API adjusted to the age and needs of the child. The intended dose volume or size should be appropriate for the target age group. Paediatric medicines should preferably be presented as formulations that are ready to administer. The need for health professionals, parents or caregivers to manipulate the dose prior to administration should be kept to a minimum. It is preferable that the dosage form is palatable in itself without any need for further modification. In addition to maximizing the acceptability and palatability of paediatric medicines it is important that they are convenient to produce and affordable.

Paediatric population constitutes special part of the society. Special care and attention is needed for this population. It is their right to get an age appropriate and suitable dosage form. Being heterogeneous in age and requirements, this group presents challenges to the health professionals. This group presents number of opportunities to health professionals for development in paediatric formulation, generation of systematic clinical studies in paediatrics, generation of safety data, and potential methods for evaluation of developed technologies and finding and evaluation of different taste assessment methods like human panel method, animal behavioral model and electronic tongue etc. This population demands extensive studies from health professionals and is the most interesting and challenging field to consider for research.

**FUTURE STEPS**

The ideal pediatric formulation should have flexible dosage increments and minimal excipients, be palatable, safe and easy to administer, and be stable with regard to light, humidity, and heat. Nevertheless, a significant number of drug formulations are unsuitable for children, which leads to unsafe off-label and unlicensed use of adult medicines. Recent initiatives promoting paediatric drug development have made some initial progress in the neglected area of pediatric formulations. Most efforts have focused on age-appropriate oral solid preparations, which enable dose flexibility, easier administration, and better acceptance in children. Despite these advances, the new paediatric formulations are still only a small part of the full therapeutic arsenal needed to serve all pediatric patients. The following 5 priorities have been identified as critical for the further development of appropriate paediatric formulations:

1. The first key issue is the continuous prioritization process that focuses on unmet public health issues and ensures that drug development aligns with the true clinical needs in children. Special attention should be paid to innovations that improve drug delivery in neonates, fill treatment gaps in pediatric cancers, and treat diseases of high burden in developing countries.
2. Second, better use of existing data are required to facilitate pediatric drug development. Some innovative scenarios under investigation include preliminary “enabling” formulations that bridge existing adult formulations and potential pediatric market formulations, adjustments of adult in vitro gastrointestinal models to study drug bioavailability in children, and refined criteria for the extrapolation of adult efficacy data to the pediatric population.

3. Third, future research on paediatric formulations could potentially benefit from existing or innovative technologies under development in adults. Novel experimental treatments of adult cancers, infections, and asthma have used nanoparticle-targeted therapy, novel smart polymer based drug delivery systems, new chemical entities (e.g., dendrimers), and remote triggering devices. These treatments may have significant applications in children, and the identification of appropriate animal models for paediatric preclinical studies should be a research priority.
4. Fourth, ongoing technologic advances need to be accompanied by relevant patient outcome studies and clinical feedback on efficacy, safety, patient acceptability, preferences, and adherence regarding new formulations; currently, such studies and feedback are lacking. Practice-based evidence on the impact of novel formulations, generated by health care professionals and caregivers, could provide further support for the development of paediatric medicines with clear clinical advantages.
5. The fifth priority concerns finance. Because innovative technologies are costly, the ultimate challenge is to make these new pediatric formulations available on the market and in daily practice. Their commercial viability might be improved by an increased market size (e.g., global scale, inclusion of geriatric patients and adults with swallowing difficulties); new incentive schemes (particularly for off-patent drugs), such as limited exclusivity and premiums, funding, and tax breaks and public–private partnerships that support the development of orphan drugs and other less profitable niches.

In short, to reach these goals, it is essential that there is a committed collaboration between stakeholders that extends across disciplines and geographic regions. Moreover, this collaboration should have the innovative potential to further shape the paediatric drug development agenda and thus to close the adult–child medicine gap.

Palatability is the most important element of patient acceptance of medicinal product. It is defined as the overall appreciation of a (often oral) medicine by organoleptic properties such as smell, taste, aftertaste and texture (i.e. mouth feel). It is determined by the characteristics of the components (API and Excipients) and the way API formulated. Palatability is relevant for other routes of administration e.g. buccal, nasal, inhalation. Thus medicinal product should have not only pleasant taste but also should have acceptable mouth feel (viscosity, grittiness) and appearance (visual aspect, size, shape, packaging). Thus palatability and indeed acceptability are key considerations when defining target product profile. The

importance of acceptable palatability has been recognised by regulatory authorities like European Medicines Evaluation Agency, French Regulatory Affairs etc. Most of APIs have an unpleasant taste. The pragmatic approach often taken by care givers and patients to facilitate dosing is to dilute or obscure taste of medicinal product by mixing or sprinkling it in food/beverages. However, there are risks associated with this approach. For example, the entire dose of the medicinal product may not be consumed especially if the volume or quantity of food/ beverage is too large or taste not appropriately masked. In addition this approach may result in the child being put off the food/beverage used, which could be a particular issue for very young children and babies where milk is the main food source. Hence mixing with food or beverage should not be the primary means of taste masking. The aim of taste masking techniques are to obscure the aversive taste of an API or formulation or prevent interaction of dissolved API with taste receptors in the mouth and throat. Different technologies have been employed for taste masking. These technologies include conventional methods and modern methods. Additions of sweeteners, flavouring agents are conventional methods to mask the taste of drug but use of these methods alone cannot mask taste of aggressively bitter drugs. Newer technologies like complexation with cyclodextrin, ion exchange resins, coating, lipid coating, etc. are now used by pharmaceutical industries for better taste masking and patient compliance.

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