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Formulation Approaches To Pediatric Oral Drug Delivery: Benefits And Limitations

R. Manikandan ,K. Lakshmi*

Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam – 603 103, Tamil Nadu, India
*For Correspondence: laxmisiva@gmail.com
ORCHID ID: 0000-0002-2460-0073

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Abstract

The goal of this study is to develop a novel oral drug delivery technique for children. The drug is made to best suit the child's age, size, physiological state, and necessary treatment to address concerns about taste preference, toxicity, and drug administration. In many areas of pharmacotherapy, pediatrics and adults are different. The largest obstacle in creating a pediatric formulation is palatability. There is a great deal of room for new research when it comes to designing the pediatric drug delivery system because of the solid formulation's numerous limitations. Innovative methods for oral drug delivery systems only partially address the problems without providing adequate answers. New and creative research is conducted to overcome these issues. The formulation ought to be made with pediatric patients' ease of administration, with dose flexibility and improved drug formulation palatability

Introduction

The wide range of clinical and pharmaceutical factors that need to be taken into account to guarantee the quality, safety, and efficacy of the finished product makes developing an age-appropriate formulation difficult. The additional needs and demands of this target population of children make the development of pediatric formulations particularly challenging. Depending on a child's developmental stage, a drug's pharmacokinetic and pharmacodynamic profile can vary significantly, so dose flexibility is necessary to meet the dosing needs of all age groups. Other factors should be taken into account when developing a formulation because excipients that are generally thought to be safe may pose a safety risk to children. Since children have different tastes and swallowing capacities than other demographic groups, palatability and ease of swallowing are also regarded as essential characteristics for the acceptability of medications meant for them. Dependency on caregivers frequently affects how medications are administered and how well they are received. Aspects of manufacturing, processing, and packaging must be taken into consideration in addition to all of the previously listed factors. To satisfy the needs of patients, caregivers, manufacturers, and healthcare providers, the perfect formulation must combine several requirements. The many elements that need to be taken into account while developing age-appropriate products have been divided into three primary groups: i) issues about patient safety; ii) factors affecting patients' access to medications; and iii) factors about efficacy and convenience of use. With the help of changes to the regulatory framework, there has been a greater emphasis in recent years on the creation of innovative technologies for the development of age-appropriate formulations. The number of formulation design techniques (such dispersible tablets, oral films, and minitablets) and administration/dosing devices (like medicated straws and minitablet dispensers) that have been studied, patented, and brought to market has noticeably increased as a result[1].**Significant Progress in Conventional Oral Drug Delivery Systems[2]**

"Liquid medication forms are essential and widely used for effective administration."

Scientists in this era shifted their focus to the development of solid dosage forms because of the wide range of

limitations that liquid dosage forms had over solid dosage forms. Because liquid dosage forms are easier to swallow and have more dose flexibility than solid ones, they can also be used in certain situations, such as with newborns. Because control release dosage forms have not been developed, liquid dosage forms must be administered several times throughout the day. Only a few sustained-release formulations are currently on the market, despite numerous studies being conducted on the development of sustained-release liquids, such as natural polymer-based resin, coated microparticles in suspension, and others. The success of these studies is frequently not maintained. In pediatric formulation, the right vehicle is essential with enhanced palatability. Milk has recently been investigated as a liquid formulation vehicle due to its high stability and solubility. Additionally, the lipid-based vehicle makes highly lipid-soluble medications more soluble. The creation of administration tools, such as baby bottles with a syringe, for the administration of liquid dosage forms, is the emerging field in liquid dosage form technology.

Solid Dosage Form[3]

Solid dosage forms are superior to pharmaceutical industry formulations due to their numerous advantages. They offer low manufacturing costs, efficient supply chain, and long-term stability. Due to swallowing issues and variable dosages, pediatric patients are generally not receptive to conventional solid dosage forms. Devices such as "pill swallowing cups" have been used to improve the appropriateness of administration in these situations. The "solid dosage pens," which resemble pens and cut tablets into tiny slices of a predetermined length, are an intriguing new development in solid dosage forms. The stability, safety, and acceptability of dosage forms are enhanced by recent advancements in the most recent packaging system. The printed blister that provides self-monitoring treatment and instructions for the correct administration of medication is part of the compliance-prompting packaging.

Fig -1 Novel Approaches to Oral Drug Delivery Systems in Pediatrics[4]

Oro-Dispersible Tablets:

Created to overcome the issue of swallowing the entire tablet, which is ODT-S, a formulation typically not tolerated by children and that dissolves quickly. The "fast dissolution and disintegration" properties aid in the development of such innovative techniques and eliminate the need for carriers like milk and water. The primary benefits of ODT-S over tablets are the avoidance of swallowing, dose flexibility, and lack of water requirement. Additionally, ODT-S provides improved bioavailability and onset of action. The fragility of ODT formulations, which may impact dose flexibility, typically contraindicates tablet splitting. "Orally disintegrating mini-tablets" are used to solve such issues.

The primary benefit of these formulations is that they provide both multiparticulate and ODT-S advantages. Medicines are primarily absorbed through the alimentary canal, but they can also be absorbed sublingually or buccally, which has advantages for bioavailability and onset of action. Some methods for creating ODT-S include lyophilization, direct compression, 3D printing, tablet molding, and the flash heat method. ODT‟ S manufacturing is tightly regulated by patented technologies. Recent ODT platforms with rapid disintegration and high drug loading are based on 3D printing technology. Examples of medications currently on the market that are ODT-S Olanzapine, Risperidone, Selegiline, Tramadol, Donepezil, and Lamictal.

Product Characteristic	Advantages	Disadvantages
Efficacy acceptability *Dosage* *Preparation*	Water is not required Swallowing is avoided Flexibility of administration Preferred over conventional formulations	Various dosage strengths require a lack of mechanical strength
Compliance		Controlled release and taste masking is challenging
Safety Profile *Bioavailability* *Excipients* *Stability* *Medication Error*	This may be improved by buccal absorption.	Excipients with unknown safety profiles and storage conditions can have critical retention time in the mouth and alter bioavailability.

Patient Access *Manufacturability* *Affordability*		High doses may not incorporate technologies subjected to intellectual property rights.

o-Dispersible[5]

ODT S is based on a polymeric matrix and are intended to create rapidly disintegrating preparations. They have the following benefits: continuous manufacturing, increased bioavailability through buccal absorption, no need for water, and no need to swallow. Limitations include difficult control of release and taste masking, difficult dose uniformity, and the need for specialized packaging. Additionally, they have a sophisticated look and more dosage flexibility due to their unique strength, which is obtained by cutting the films to the proper size. Since they are made for quick adherence to the buccal mucosa and prompt drug release, their fast-dissolving advantage is no longer for intentional activity. They are usually made using the solvent casting method and consist of a polymeric matrix with the drug embedded in it. Hot-melt extrusion is an alternate technique that avoids the use of solvents and is advantageous for controlling release and masking film taste. Only potent medications with particular physicochemical characteristics can be readily administered in the developing era due to restrictions on dosages greater than 100 mg, which are advantageous for novel techniques like electrospinning and inkjet printing. ODF is sealed separately to increase stability and lower the possibility of overdosing, which also reduces the likelihood of film sticking. Patients typically receive it in single-dose or multidose sachets that resemble stamp-like strips.

Product Characteristic	**Advantages**	**Disadvantages**
Efficacy, acceptability. *Dosage* *Preparation*	Excellent dosage flexibility. The product does not require. The product can be administered without swallowing.	Achieving controlled release and taste masking is challenging.
Compliance	May be preferred over conventional formulations.	
Safety Profile *Bioavailability* *Excipients* *Stability* *Medication Error* *Patient Access* *Manufacturability* *Affordability*	The product's performance may be improved through buccal absorption. The product's performance may be improved through buccal absorption. The potential for medication errors related to the product is discussed. Patient access to the product is discussed. Continuous manufacturing can be achieved. The product's performance may be improved through buccal absorption. Continuous manufacturing can be achieved.	Excipients of unknown safety profiles may require specialized packaging. Retention time in the mouth may alter bioavailability. Uniformity of dose may be challenging. Only low doses can be incorporated into technologies subjected to intellectual property rights. Solvent-based manufacturing process.

Multiparticulate drug delivery system[6]

A multiparticulate drug delivery system is intended to provide patients with greater acceptability than traditional dosage forms, such as tablets and capsules. It is made up of several separate components, including minitablets, granules, and pellets. Additionally, it is always appropriate for taste masking and controlled release. Multiparticulate drug delivery systems have several benefits, including easy functionalization, great dose and administration flexibility, easy access to manufacturing technology, a targeted release profile, appropriate taste masking, highly reproducible bioavailability, and easier swallowing due to smaller size. The restrictions are changes in mouthfeel and grittiness, and bioavailability as a result of co-administration with meals and beverages. To equip metered accessories, special administration is required. A packaging and dosing platform must be

developed. Studying food-drug compatibility is necessary. Oral gels and in-situ gelling vehicles are being researched as potential aids for the administration of multiparticulate formulations. Water, applesauce, and milk could all be utilized as delivery vehicles for these formulations. According to recent studies, milk and yogurt work best for pediatric formulations. A polymeric coating step is typically included in the manufacturing process as a downstream processing step to improve controlled release and taste-masking properties. It provides a great deal of flexibility in terms of presentation and packaging. The formulations are frequently encapsulated to facilitate easy use by patients. Additionally, granules and pellets can be integrated into medical devices to improve administration. Medicated spoons and dose-sipping technology are two examples of administration devices. While precise dosing is limited, volumetric spoons are generally a cost-effective method. More advanced equipment is required for more precise and effective dosing. In general, the development and scaling of these technologies may also be more expensive.

Product Characteristic	Advantages	Disadvantages
Efficacy, acceptability *Dosage* *Preparation*	Excellent flexibility of dose Small sizes/ swallowing is aided Flexibility of administration Ease of functionalization Suitable for taste masking	Grittiness/mouthfeel may be an issue Need for preparation/ reconstitution
Compliance	Highly reproducible due to uniform GI transit	Co-administration with food/drinks may alter bioavailability
Safety Profile *Bioavailability* *Excipients* *Stability* *Medication Error* *Patient Access* *Manufacturability* *Affordability*	A targeted release profile can be achieved Use of generally regarded as safe [GRAS] excipients Manufacturing technology readily available	Food drug compatibility needs to be studied Limited control over dose intake when mixed with food May need specialized equipment for accessories Need to develop packaging/dosing/technology platform

hewable formulation [7]

Chewable formulations, such as chewing gum, soft chews, and chewable tablets, are made to help the API dissolve and disintegrate more effectively. These formulations are typically made with hydrophilic sweeteners, such as mannitol, which has a pleasant, cooling taste, avoids the need for swallowing, does not require water, and may even be preferred over traditional formulations. Buccal absorption and the availability of manufacturing and packaging technologies may also enhance bioavailability. The need for chewing may restrict the use of these formulations in pediatrics, although two-year-olds frequently tolerate them well.Having certain restrictions It can be difficult to mask taste and regulate release; different dosage strengths might be needed; and there might be specialized devices and accessories (equipment). Chewable tablets are usually made using a compression method, which is similar to ODT-S, but these formulations do not use disintegrants. Furthermore, patients may choose to prefer these formulations rather than relying on the explanations of other formulations for their diverse range of aesthetic qualities. Additionally, some technologies for the production and preparation of chewable dosage formulations are patented. For instance, tablet molding was supported by the Paulsen method, where heat and water use are minimized. Soft gelatin capsule technology that has been altered by the use of chewable fillers supports another technology. It provides the benefit of soft gel without requiring the entire capsule to be swallowed.

Product Characteristic	Advantages	Disadvantages
Efficacy acceptability *Dosage*	Water is not required Swallowing is avoided	Various dosage strengths required.

Preparation	May be preferred over conventional formulations.	Controlled-release is challenging. Taste masking is challenging.
Compliance	This may be improved by quick disintegration and dissolution. This may be improved by buccal absorption.	Bioavailability may be altered depending on chewing ability.
Safety Profile *Bioavailability* *Excipients* *Stability* *Medication Error* *Patient Access* *Manufacturability* *Affordability*	Manufacturing and packaging technology are readily available.	Excipients of unknown safety profiles may be required . Soft chews may be problematic due to water content. Retention time in the mouth may alter bioavailability. . Possible overdose if misused as confectionery. May need specialized equipment or accessories.

CHALLENGES[8]

The development of palatable formulations is fraught with difficulties since the palatability of age-appropriate oral medications is essential for adherence to therapeutic control.

Challenges associated with developing palatable formulations:

The formulation's delicacy was given top priority during the development of the pediatric formulation. Masking the taste of the active pharmaceutical ingredient (API) in a formulation is a difficult task because the patient may not recognize the taste of the API during administration. The inability to make an in vitro determination is one of the biggest drawbacks of delicacy evaluation. There are differences in the perception of the delicacy of medication between adults and children, as well as between healthy and sick children. As a result, only children were used in the clinical study; however, there are certain ethical problems with clinical trials involving children. The "swill and spit" method is therefore useful for evaluating palatability. However, the "swill and spit" technique can be used unethically with healthy volunteers. For instance, it is deemed unethical to test drugs for cytotoxicity in healthy volunteers. Researching the acceptability and palatability of medications in children is challenging in these situations (Anne Cram et al., 2009). Alternatively, palatability can be evaluated when patients are prescribed medication regularly instead of just once. In practice, formulation issues arise from a lack of testing and assessment methods. Delicacy evaluation issues can also be resolved by considering child-favorite flavors, such as cherry, chocolate, apple, and strawberry, which can be added to the liquid formulation to boost its acceptability.

Challenges associated with advancements in medicine and improvements in formulations: [9]

The primary focus of developing the novel oral administration dosage form is on formulation properties that are relevant to the development of the conventional dosage form for adults. Oral solid dosage forms are preferred by younger and older children, while liquid dosage forms are preferred by smaller children. At the time of formulation development, physical and physicochemical parameters are prioritized over taste. The drug's solubility properties are a very challenging property to develop when creating the pediatric formulation. It is challenging to hide the taste of a drug with highly soluble properties and create a liquid dosage form, like a suspension, because the drug is highly soluble and readily dissolved in the mouth. As an alternative to these circumstances, drug coating and the creation of film-coated mini tablets and pellets are done. The demands of industry, healthcare providers, patients, and caregivers make it difficult to develop pharmaceutical products that are age-appropriate.

Conclusion[10]

The demands of industry, healthcare providers, patients, and caregivers make it difficult to develop pharmaceutical products that are age-appropriate. Many age-appropriate products have been researched, created, and patented over the last 20 years, and some have even been approved for sale. This manuscript has reviewed the current approaches to the development of age-appropriate oral drug delivery systems. The rational choice of one formulation approach over another is unfortunately hampered by the paucity of data on the acceptability and

patient preference of emerging dosage forms (such as ODTs, ODFs, chewable formulations, multiparticulates, and minitablets) for the various age subgroups. A single formulation approach is unlikely to be suitable for all pediatric patients due to the diversity of the pediatric population and the discussed limitations of the current technologies. For every product, the choice of an appropriate formulation strategy for a specific population group must be carefully considered. To enable a correlation between the development of technological features and patient acceptability that directs such a selection process, more research in this area is desired.

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