Review Article

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Advancements in Formulation Approaches to Pediatric Oral Drug Delivery Systems

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ABSTRACT

Designing and developing pediatric formulations is a challenging task as different patients have varied needs. Drug administration, flexibility, patient compliance, palatability, toxicity are the factors that are required to be considered during the development of pediatric preparations. To overcome the drawbacks of conventional drug delivery systems, the researchers have focused on various innovative methods such as novel drug delivery systems (NDDS). NDDS focuses on the formulation and development of pediatric formulations considering tolerability, efficacy and safety of active pharmaceutical ingredients and excipients.

Keywords: Pediatrics; Palatability; Formulation; Oral drug delivery; Novel drug delivery system

1. INTRODUCTION

Oral drug delivery systems are the age-appropriate drug delivery systems that are explicitly designed to enhance the feasibility of drug administration in especially in children [1]. Since conventional preparations are not tailored for the particular patient population, patient-centric formulation design is aimed towards addressing compromised visual, physiological and motoric capacities that will not only favour pediatric but also geriatric patients in terms of acceptance and consistency [2]. In case of pediatric population, pharmacokinetic and pharmacodynamic profile of drugs varies greatly depending on a child's growing period hence dose flexibility has become essential trait to meet the needs of all pediatric age groups [3]. Appropriate excipients, ease of swallowing and palatability are the other censorious parameters required to be considered during formulation of pediatric oral dosage forms. Children have different taste habits and swallowing capacity than other subsets of the population, so this is a vital trait for the permissibility of medicines intended for them. In several cases, caregiver dependency affects medication acceptability and administration [4].

Production and packaging logistics are also important aspects of concern apart from the aforementioned factors. Pharmaceutical production processes must be reliable and capable of producing high-quality medicines at a reasonable cost. Packaging and administering devices should be made an essential part of the product because they can increase the consistency and acceptability of medication and compliance keeping the expenses to a minimum [6,7].

With a broad variety of pharmaceuticals and therapeutic aspects such as safety and efficacy, the evolution of pediatric as oral drug delivery systems is difficult. So the innovative drug delivery systems are intended to overcome issues related to physiological disability and swallowing difficulties. The pharmacodynamic and pharmacokinetic parameters of a medication changes as a child grows, necessitating additional modifications in dosage which can be fulfilled by oral formulation, hence patients may find oral formulations to be fair and convenient [1].

Several research organizations continue to conduct research and campaign technological advancements in the areas of pediatric oral drug delivery systems. Educational domain of medicine and the pharmaceutical industry have shaped the Food and Drug Administration (FDA) and created Pediatric Formulation Initiative in the United States (US) to encourage pediatric formulation study under science and technology. For the design and development of novel pediatric formulations, World Health Organization (WHO) has initiated a global campaign called "*Make Medicines Child Size"* to promote the creation of drug delivery systems for children [7].

2. NEW DEVELOPMENTS IN CONVENTIONAL ORAL DRUG DELIVERY SYSTEM

2.1 Liquid dosage forms

The main focus of liquid dosage form is to convert dry solid formulation into liquid formulation for the ease of administration. As liquid dosage forms are facing some problems like incompatibility, instability, high cost of transportation and it also requires multiple-dose. The failure of controlled release formulations is one of the major drawbacks of liquid dosages forms in terms of patient acceptability. So to overcome these problems researchers are moving towards formulations of solid dosage forms. Owing to the improved dose versatility, liquid formulations may be preferable for children, infants and neonates in contrast to solid materials because of ease of administration [1].

Recent research has focused on finding suitable vehicles for pediatric preparations with an increased ability of masking the bitter taste. Milk has been investigated as a carrier for liquid products with positive results in terms of high stability and solubility [8,9]. Lipid-based vehicles also enable for the solubility of highly lipid-soluble drugs as well as palatability [10]. For the production of sustained-release liquids, a variety of methods have been investigated, including drug microemulsions, coated microspheres in suspension and ion exchange resins [11,12]. Examples of extended-release oral suspensions include Azithromycin Extended Release (Zmax® by Pfizer) and Methylphenidate Hydrochloride Extended-Release [13].

Dose sipping syringe, modified pacifier, a baby bottle with a syringe are some delivery devices used in liquid dosage forms [14,15]. The nipple shield device is built to fit an insert containing a drug that delivers the API into milk when nursing newborns (Figure

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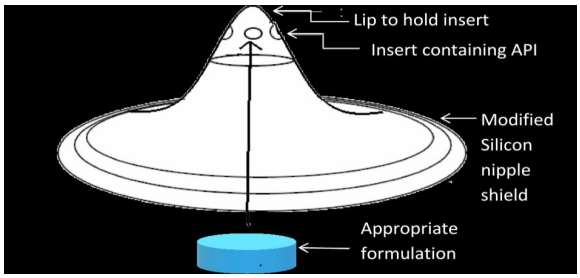

Figure 1. Nipple Shield

1) [16,17]. The total cost of the system is the major obstacle to the broader use of these delivery devices.

2.2 Solid dosage forms

The main focus of solid dosage forms is to increase the versatility of a single-unit dosage form. Solid formulations are advantageous over other dosage forms as they provide long term stability, accurate dose, easy shipping and handling and low cost of manufacturing. They have certain benefits over liquids, such as superior consistency, less weight and are suitability for individuals of all ages, even those who have trouble swallowing tablets. But conventional solid dosage forms cannot be appropriate for pediatric patients because of palatability problems and swallowing difficulties. The lack of dosage flexibility in the conventional solid dosage form is the main drawback.

Smaller capsules and tablets are emerging as a viable substitute for conventional solid dosage types, leading to greater dose flexibility and thus easier swallowing. Minitablets have been developed for ease of administration to pediatric patients. Numerous studies have shown that infants of 6-12 months can swallow a single 2mm minitablet easily[18,19]. Despite this, the effective dose that the delivery of singular minitablets is constrained by their small dimensions. Desitin® minitablets (levetiracetam), Orfiril® (sodium valproate sustained release), KALYDECO® (ivacaftor) and LAMISIL® (terbinafine hydrochloride) are the few examples of marketed products.

Kayitare et al., have developed an eight-segment tablet [20], while Kalpan and Solomon developed a new technique for the development of tablets having no API to assist sufficient separation without sacrificing delivered product accuracy [21]. Despite the protection and effectiveness risks, pill splitters (Figure 2) are more commonly used [22,23]. Tablets and capsules of a comparatively large scale have been

Figure 2. Pill splitter

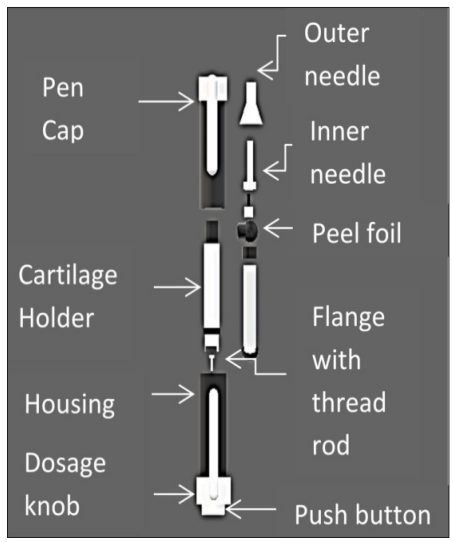

Figure 3. Solid dosage pen

made more suitable for a wider population by using a delivery device such as pill swallowing cups [24]. The solid dosage pen is made up of a mass-extrusion-produced cylindrical rod that is implanted into a device which is like a pen, is an intriguing creation that works by slicing tiny tablet-like strips, dosing changes can be made of the necessary length (Figure 3) [25,26].

New solid dosage shape packaging systems are now being developed with the goal of strengthening medicine protection and acceptability. Compliance-inducing packaging includes handwritten blisters for self-monitoring of the procedure (calendar packaging) as well as instructions for proper use of administration,

which when combined with necessary information factors and other reminder techniques, if necessary, can help with medication compliance [27].

3. NOVEL ADVANCES TO PEDIATRIC DRUG DELIVERY SYSTEMS

To overcome problems occurring in conventional drug delivery systems, scientists have developed novel drug delivery systems for pediatrics. Multiparticulate drug delivery system, orodispersible films (ODFs), orodispersible tablets (ODTs) and chewable formulations are some novel approaches designed for new formulations.

3.1 Multiparticulate drug delivery systems

Multiparticulates are made up of a number of easy-to-swallow and small units. These formulations are now made in unit doses, which are either opened before administration or swallowed whole. According to recent FDA advice, the maximum size of the goal should be 2.5 mm for patient acceptability of multiparticulates [28]. The examples of multiparticulates include pellets, granules and minitablets. Because of their smaller shape and size, multiparticulate formulations are expected to have higher patient acceptability than tablets and capsules. Being single unit dosage forms they provide enhanced swallowing ease as well as improved multi-unit composition and flexibility of dose. Multiparticulate dosage forms are frequently suited for taste masking through film-coating techniques and controlled release, which can help in enhancing the patient compliance. Multiparticulate formulations are becoming more preferred pediatric dosage forms.

In situ gelling and oral gels have also been reported in several research investigations as useful media to help administer multiparticulate formulations [29]. Multiparticulates may be given directly into the mouth of the patient or, if preferred, dispersed in a vehicle before being administered. Widely accepted vehicles are water, apple sauce or juice and milk [30]. Multiparticulate administration with food is sometimes recommended to enhance organoleptic properties. Food or beverages raise safety issues, such as a lack of dosage regulation and a negative effect on medication bioavailability [31]. Albertini et al. examined the solid lipid compatibility where milk and yogurt contain microparticles that can be used as delivery vehicles for children [32].

Multiparticulate formulations can reduce the repeated administration of dose and also avoid the risk of dose-dumping and improve the stability, bioavailability, flexibility of dosage forms during administration [33]. Apart from this, manufacturing technology is readily available so good affordability is another added advantage of multiparticulate formulations.

There are various pelletization techniques used to prepare the multiparticulate formulations (Figure 4). In order to minimize variability and cost in the man-

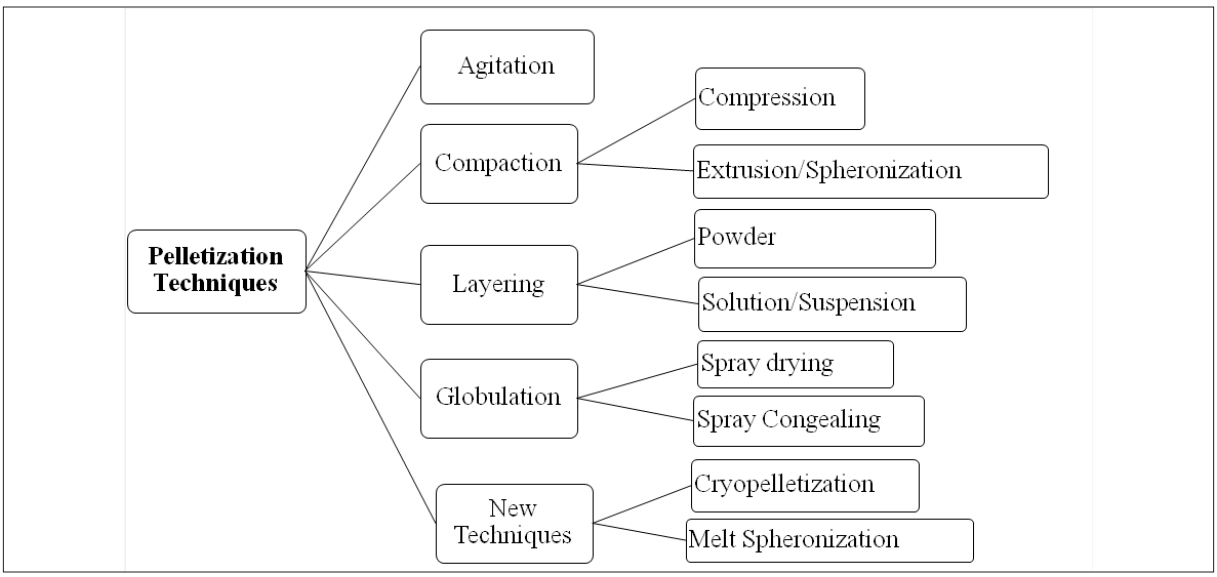

Figure 4. Techniques for pelettization

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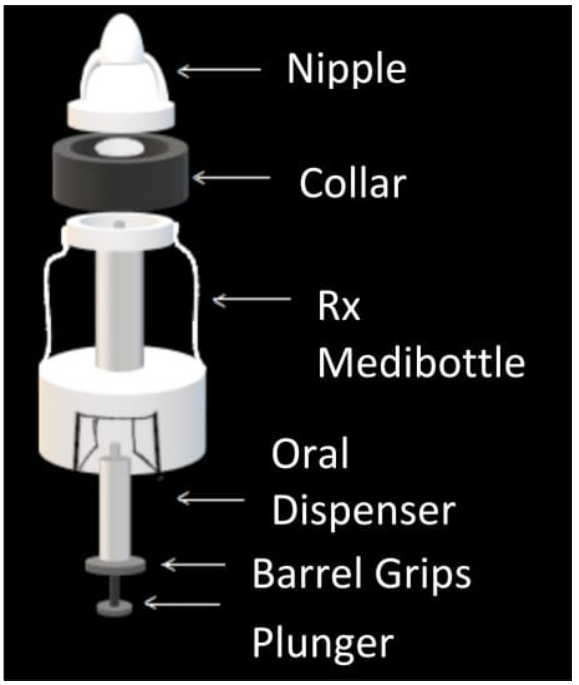

Figure 5. Medibottle

Figure 6. Dose sipping straw

ufacture of adolescent medications, one-step process (direct pelletization) is more preferred as compared to multi-step procedures [34]. A polymeric coating stage is typically included in the manufacturing of multiparticulate formulations as a processing stage for enhanced aesthetic properties, taste masking and controlled release in the process of functionalization.

Multiparticulates also provide a lot of options when it comes to packaging and presentation. These preparations can be loaded into capsules, unless introduced to the patient as an easy-to-open capsule, this could restrict their swallowing advantage [35]. Furthermore, single-dose sachets of multiparticulate products may be prepared, leading to higher doses than capsules and tablets.

To aid administration, granules or pellets may be inserted into delivery devices. A new oral syringe (Sympfiny TM, NJ, Morristown) is developed for use in dispensing and administering multiparticulate preparations to pediatrics. This oral syringe was tested in forty children aged between 4 to 12 and were given 2.0, 1.2 and 0.5 ml doses of placebo multiparticulates through the oral syringe filled with freshwater or fluid of choice of children. Acceptability was measured by the ability of participants to swallow the dose completely and the scored dose acceptability was found to be on a 5-point scale [36].

Medicated spoons include a granulated single-dose formulation which can be distributed until administration in a liquid or immersed in any beverage to make a simple administration of pulp [37]. Dose sipping technique is a granulated product prototype straw in a glass containing water to one side, removable cap to another side and without a cap (Figure 5). In dose sipping technique, a straw used as ready to use delivery device is filled with powdered drug (Figure 6) [15]. This technology was commercialized for oral administration of clarithromycin which is an antibiotic, however, because of commercial restrictions; the product's availability was minimal later and existed only for a couple of years on the market.

Delivery devices are used to enable dose adjustment by monitoring various volumes of multi-unit particulates from a pre-filled multi-dose package. Several research activities have been conducted in this direction numerous patents have been filed for devices like electronic dispensers and medicated spoons [6]. Volumetric spoons seem to be the most expensive tool in general, but their ability to gain accurate oral doses is minimal. Highly sophisticated delivery devices are required for improved and more accurate dosing. In order to minimize the cost, the potential of these devices to handle distinct formulations with

different sizes or shapes is desirable [7].

Multiparticulate technique is used in different drug delivery systems like ophthalmic, buccal, nasal and transdermal. This delivery system is also used for conversion of oil and other lipids to solid and for easy and safe handling of toxic substances. Multiparticulate drug delivery is most applicable in improvement of odour and taste of dosage forms as it involves coating of the dosage form. Marketed products of multiparticulate drug delivery include Losec MUPS® (Omeprazole), Toprol XL® (Metoprolol), Prevacid Solutab® (Lansoprazole) and Theodur® (Theophylline) [10].

3.2 Orodispersible films

Orodispersible Film (ODF) is a type of oromucosal preparation which is defined as "single or multilayered sheets of suitable materials, to be placed in the mouth where they disperse rapidly" as per the European Pharmacopoeia [38]. Ginnola et al. defined ODF as "A thin flexible, non-friable polymeric film having dispersed active pharmaceutical ingredient which is intended to be placed on the tongue for rapid disintegration and dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract" [38].

ODFs are elegant, extremely thin, colourful and postage stamp-sized. They are available in different shapes like oval, rectangle, square, U-shaped films or in strip forms [38]. When an ODF comes into contact with saliva in the mouth, it quickly dissolves [39,40]. The rapid dissolution of ODFs in the oral cavity, close to that of their counterpart ODTs, aids swallowing and eliminates the requirement for water in their administration. It is ideal for dysphagic children and geriatric patients who are afraid of swallowing. They are beneficial to particular cases such as patients suffering from nausea and vomiting, cancer patients receiving chemotherapy, mentally disturbed, bedridden, uncooperative patients and patients with Parkinson's disease [41]. ODFs provide an added advantage over tablets in terms of dosage versatility, since various strengths are being accomplished by easy cutting of films to the size of need [42].

Major drawbacks of ODFs such as palatability and managed release are difficult to achieve technologically. The use of coating methods for to fulfil these objectives is restricted by the inherent design of manufacturing process, which typically requires solubilization of the API [42]. For achieving this, drug absorption via the oral mucosa has been reduced, resulting in controlled release. ODFs have been used nowadays for topical drug delivery instead of systemic drug delivery [43].

ODFs are made up of a drug-containing polymeric matrix and they are usually made using the solvent casting process. The solvent casting process, which is suitable for both laboratories and industries, is the most commonly used easy and straightforward technique of ODFs. Hot-melt extrusion, electrostatic powder deposition and electrospinning are some of the other techniques. Modern ODF preparation techniques rely on 2D and 3D printing technologies such as continuous fused deposit printing, flexographic printing and ink-jet printing [44,45]. Due to the thickness (25 µm - 2 mm) and small size (2 to 9 cm^2) of the ODFs, the amount of medication that can be filled is very minimal (typically <60-70 mg). While modern inventions allow for maximum drug doses of >100 mg [46], this quantity is still small, because only potent drugs with unique chemical and physical properties can be delivered successfully [47]. Steiner et al. In his recent publication described about SOFTs (Structured Orodispersible Film Templates), which are modern ODFs with the significant potential drug content, with the lower portion covered and the upper porous layer filled with the appropriate drug before being sealed with a polymer film [48].

The requirement of specialized manufacturing and packaging equipment can render the development of ODFs less viable [49]. ODFs such as breath fresheners, vitamins and food supplements, cough suppressants and anti-histaminics are the most common and widely used ones [50]. Ondansetron oral-soluble film was the first prescription-only ODF to hit the market, with indications for adults and children of age above the four years in the USA [51]. Rodd et al. published relative studies on the acceptability of oral filmstrips and drops as a source of vitamin D. When opposed to oral Vitamin D drops, 85.4 % of parents and infants favoured the use of filmstrips, according to the report [52,53]. Some of the orodispersible films include Ramea® ODF (Ramosetron), Rizaport® (Rizatryptan), Gas-X® (Symetykon), Zyris® ODF (Tadalafil) [51].

3.3 Orodispersible tablets

WHO has recommended the production of flexible

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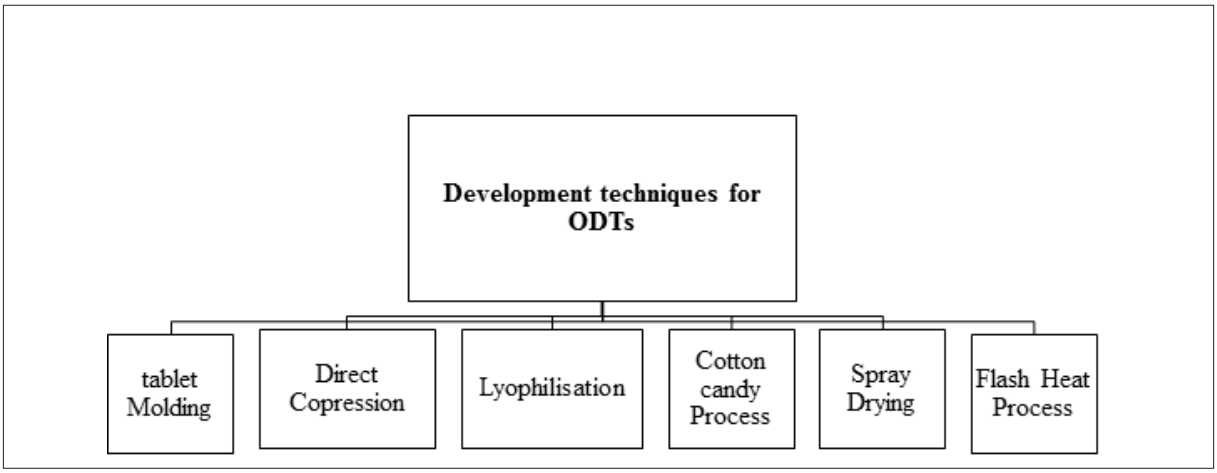

Figure 7. Development Techniques for ODT's

oral solid dosage forms, such as tablets which can be dissolved or dispersed in a solvent before administration [54]. ODTs are formulated to disintegrate in the mouth in a fraction of a second, eliminating the need to chew the entire tablet [55]. Super disintegrants, such as carboxymethyl cellulose, cross-linked cellulose imitative, polyvinylpyrrolidone, sodium starch glycolate are added to ODTs to provide rapid breakdown when in contact with salivary secretions or water. Because of pregastric and oral absorption, drug bioavailability can increase, thus reducing the first-pass metabolism in the GIT [56].

ODTs have better stability than semi-solid or liquid dosage forms. Drug loading is very high in the case of ODTs. It is non-complex and doesn't require any measurement device (e.g., oral syringe, or dosing spoon) while administration [54]. The bioavailability of hydrophobic and insoluble drugs administered in the form of ODTs increases due to the gradual dissolution and disintegration of the tablets. In pediatric patients, dispersible dosage forms containing multiple excipients have an appropriate safety profile, so preservatives are not required to be used [55].

Furthermore, due to the brittleness of ODT preparations, tablet splitting is normally prohibited, limiting dose flexibility even further [49]. These drawbacks could be solved by creating 'orally disintegrating minitablets', an intriguing approach towards enhancing the advantages of multiparticulates and ODTs [57]. To ensure appropriate palatability, sweetener and flavour may be needed. Coating drug particles is an efficient method of masking flavour, but it is more difficult technically [58,59]. The effectiveness of this technique with the use of such excipients is frequently limited because of the safety concerns (particularly in pediatric patients) [58]. Nonetheless, proprietary ODT approaches have shown their ability to fix this problem by preparing and compressing microencapsulated drugs from polymer-coated drug particles for a more personalized release with enhanced organoleptic properties [60].

Direct compression and lyophilization are manufacturing processes that are commonly used for ODTs. Lyophilized ODTs are more mechanically fragile than compressed tablets. To ensure stability, compressed ODTs also require advanced packaging. Lyophilized ODTs disintegrate faster (often in less than 10 seconds) than compressed tablets (Figure 7). The recommended dosage that can be administered with lyophilized ODTs normally is 60 mg for the water-soluble drug and <400 mg for the poorly water-soluble drug [61]. Furthermore, developing compressed ODT formulations can be time-consuming, as it can be difficult to strike the appropriate balance between adequate mechanical strength and rapid disintegration [61].

ODTs may be developed considering broad variety of dosages, release profiles, geometries, and sizes by simply changing a digital model, allowing patients to receive personalized treatments. Modern ODT design is focused on 3D printing, which allows for the development of 'sponge-like tablets' with fast disintegration of fewer than 10 seconds and loading of the drug up to 1000 mg, overcoming a few of the drawbacks of lyophilized and compressed ODTs [47]. Patented technologies are used to tightly regu-

late the processing of ODTs. The novel technology in ODTs is a fast dissolving technique focused on a consistent "form-fill-freeze" system of lyophilized doses concentrated in blisters. Other ODT methodologies have been applied using patented compression or lyophilization techniques and marketed under various trade names [62].

The percentage of ODT products is rapidly increasing in the market considering the high costs involved in the formulation and manufacturing of ODTs, which are mostly exposed to expensive manufacturing and packaging stages and are given to IPR [1]. While the majority of these drugs are intended for teenagers and adults, pediatric ODT formulations are becoming more common. To protect the dosage of ODTs, special packaging is needed during production and storage. On the basis of application and marketing goals, the system may be packaged in a variety of ways, including a blister card with several units, a single pouch, a continuous roll dispenser and a multiple unit dispenser [56].

A newly promoted ODT is approved for one-year-old children; the medication may be mixed with water for administration through a nasogastric tube or an oral syringe or administered directly into the mouth of the patient [63]. Some of the marketed ODTs are Imodium Lingual® (Imodium), Pepcid RPD® (Famotidine), Zyprexa Zydis® (Olanzapine), Zofran® ODT (Ondansetron), Remeron Soltab® (Mirtazapine), Feldene® Melt (Piroxicam), Maxalt-MLT® (Rizatriptan), Claritin Reditab® (Micronized Loratidine), etc. [62].

3.4 Chewable formulations

Chewable preparations such as soft chews, chewable tablets and chewing gums are all made to be processed mechanically in the mouth to help the API disintegrate and dissolve [1]. Chewable tablets are the tablets that are intended to be chewed in order to allow the release of active ingredients. These formulations have the benefits of assisting swallowing and need no water for administration. In the case of ODTs, as compared to conventional tablets, chewable formulations might not have a benefit in terms of dosage flexibility. Chewable tablets have benefits of portability, manufacturability, long-term stability and dosing accuracy as a dosage form.

The patient aids in swallowing and disintegration of chewable product types by sucking and chewing. As a result, mouthfeel and taste become vital attributes, necessitating careful consideration of excipient selection [64]. To enhance palatability, sweeteners and sugar-based fillers including sorbitol, sucrose and mannitol are mostly used. Chewable formulations show a particular controlled release through coating methods with poor adequacy for palatability, as the formulation is put under a lot of mechanical stress during administration. Furthermore, the therapeutic effect and mechanism of drug release are influenced by the patient's capacity of chewing, which can lead to inter- and intra-individual variations.[63]

The requirement to chew the formulation may restrict the applicability of chewable formulations in the pediatric population. Chewable tablets on the other hand have been reported to be healthy and well-tolerated in children as young as two years old [65]. The gum-based core is not intended to be swallowed, unlike chewable tablets. As a result, the time necessary to attain full API dissolution must be calculated and reported on the product description. Chewing gum is only recommended for children of age 6 or older due to lack of guaranteed children safety. Furthermore, some statements have been made about the potential abuse of these items, which could be consumed as confectionery items by pediatrics [66].

Chewable formulations are formulated by compression in the same way as compressed ODTs but no disintegrants are used in products. Many chewable formulations lack disintegrants or super-disintegrants, which could result in extended dissolution if not chewed. Fast dissolution or disintegration, on the other hand, is an important factor in cases where person swallows a tablet without chewing. Paulsen et al. on the basis of tablet moulding described a manufacturing process wherein high temperatures and use of water are avoided [67]. Other methods rely on the use of chewable filler enhanced soft gelatine capsule technology, which provides the advantages of soft gels without requiring the capsule to be swallowed whole [68,69]. Elastomers, waxes and artificial resins are added to the formulation before extrusion or compression to make pharmaceutical chewing gum. Drugs including chlorhexidine and fluoride have been successfully delivered locally using gum-based tableting innovation [70]. Chewing antacid tablets rather than swallowing them offers a quicker and a more reliable relief, according to Ritschel and Koeleman. Claritin® (Loratidine), Montair® (Montelukast), Lamictal® (Lamotrigine), Tylenol® (Aceta-

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minophen), Mylanta® Gas (Simethicone) are some marketed products containing chewable formulations [68].

4. CHALLENGES IN ORAL DRUG DELIVERY SYSTEMS

The palatability of age-appropriate oral medications is critical for adherence to clinical supervision, but developing palatable formulations is fraught with difficulties [71].

4.1 Challenges related to delicacy valuation

Priority is given to the delicacy of formulation while designing pediatric formulations. Since the patient would never know the taste of the API during administration, masking the taste of API in preparation is a difficult task. One of the most significant disadvantages of delicacy valuation is the lack of in vitro testing [71]. The intellect of medicine delicacy varies between adults and children, as well as between sick and healthy children. As a result, clinical trials were conducted only in children, but certain ethical issues arose in clinical trials. Hence the 'swill and spit' approach is useful for determining delicacy. However, in some cases, balanced volunteers, as well as 'swill and spit' techniques are not used ethically. Anne cram et al. stated that the acceptability and palatability of drugs are hard to understand by the pediatric patient [72]. On other hand, rather than administering a single dose, it can be valued by prescribing medicine to patients on a regular basis. In reality, problems in formulation exist due to a lack of evaluation techniques. Difficulties with delicacy valuation can also be overcome by considering flavours that children enjoy, such as chocolate, cherry taste, strawberry and apple, which when incorporated into a liquid preparation can enhance its acceptance.

4.2 Challenges related to medicine and formulation improvement

The key focus during the development of an innovative formulation used for oral administration lies on appropriate formulation properties for adolescent dosage forms with the aim of creating a conventional dosage form. Younger and older children mostly prefer oral solid formulation while infants prefer liquid formulations [71].

Taste is not a concern while designing a formulation as physicochemical and physical parameters are considered as factors of precedence. Solubility properties of drugs are challenging to establish pediatric formulations. When the solubility of the drug is high, masking the taste of the drug and formulating suspension (a liquid formulation) may be complicated since it is easily soluble in a vehicle. Due to the high solubility of the drug, which readily dissolves in the mouth, taste masking in solid dosage forms such as ODTs and chewable formulations is also challenging. Hence drug coating, formulation of film-coated pellets and mini tablets have aroused as alternative approaches.

5. CONCLUSION

The global health community must seize every opportunity to remedy the disparities in access to medications that fulfil the demand of pediatrics with a huge potential for long-term health benefits. In order to meet the demands of healthcare professionals, patients, caregivers and industry, the development age-appropriate pharmaceutical products has been difficult. The plan of action for pediatric formulations has been studied more effectively. It is concluded that solid dosage forms are used more over liquid dosage forms in the case of conventional drug delivery. The obstacles faced in the conventional system can be overcome by novel drug delivery systems. Unfortunately, the lack of data on the patient preference and acceptability of novel pharmaceutical formulations such as minitablets, multiparticulates, ODFs, ODTs and chewable formulations in various age subgroups makes reasonable formulation approach development difficult.

Different attractive devices can be used for patient acceptability and compliance. Stability, toxicity, flexibility, safety parameters can be improved by using such innovative techniques for pediatric oral formulations. For an individual product, the selection of an appropriate formulation for a targeted demographic group must be carefully considered.

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