Orally disintegrating drug carriers for paediatric pharmacotherapy

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A B S T R A C T
Non-compliance, dosing inaccuracy, choking risk, flavour, and instability, are some of the issues associated with paediatric, oral dosage forms — tablets, capsules, solutions, and suspensions. Orally disintegrating drug carriers, a dosage form with growing interest, are thought to overcome several of the challenges associated with these conventional formulations by rapidly disintegrating within the buccal cavity without the need for water. This review serves as an up-to-date report on the various types of orodispersible delivery systems, currently being developed or commercialized, by detailing their characteristics, manufacturing processes, and applications in the paediatric population. Mentioned are orodispersible tablets, films, wafers and lyophilisates, mini-tablets, capsules, granules, electrospray fibers and webs. Also highlighted are the choice of excipients, quality control requirements, and expected pharmacokinetics of orally disintegrating drug carriers concerning the paediatric population. Overall, orodispersible formulations, particularly tablets, films, and lyophilisates/wafers, have shown to be a valuable addition to medication administration in minors, thus the execution of more targeted research and development activities is expected to lead to enhanced paediatric care and outcomes.

1. Introduction

Despite continuous advances in healthcare services worldwide, childhood illness remains a cause of significant distress and burden (Golics et al., 2013). Up to one out of every four children are thought to be affected by a chronic medical condition while up to 80% of deaths under the age of five are due to infectious disease and neonatal conditions (Compas et al., 2011; World Health Organization, 2022). Examples of illnesses resulting in death in paediatrics include pneumonia, diarrhea, malaria, and meningitis (World Health Organization, 2022). It is believed that many of these deaths could be prevented with proper medical treatment and care (World Health Organization, 2022). In addition to their physical symptoms, both acute and chronic health conditions in paediatrics can have other negative consequences. Financially, childhood illnesses can lead to increased costs for both the families and healthcare system. Further consequences include decreased access to education, social isolation, and increased levels of stress (Golics et al., 2013). Thus, it is essential that effective measures, such as medication and medical procedures, are globally used to minimize the impact of childhood illnesses.

The term ‘paediatric patients’ is used to denote the subset of the population from birth to the age of 18 to 21 depending on the reference standard employed (US FDA, 2000; Williams et al., 2012). The paediatric population is often divided further into different classes based on age group. While there are inconsistencies on how these age groups should be categorized, a commonly used grouping was provided by the 2000 International Congress on Harmonization (ICH) E11 guidance for paediatric clinical trials (United States Food and Drug Administration (US FDA)), 2000; Job et al., 2019). According to these recommendations, the paediatric population can be divided into five age groups: (i) preterm newborn infants, (ii) term newborn infants (0 to 27 days), (iii) infants and toddlers (28 days to 23 months), (iv) children (2 to 11 years) and (v) adolescents (12 to 16-18 years (dependent on region)) (US FDA, 2000). Another frequently followed classification system used was provided by the National Institute of Child Health and Human Development (NICHD) which divided the paediatric population into eight age groups: (i) preterm (birth <37 weeks postmenstrual age), (ii) term neonatal (birth - 27 days), (iii) infants (28 days - 12 months), (iv) toddler (13 months - 2 years), (v) early childhood (2 - 5 years), (vi) middle childhood (6 -11 years), (vii) early adolescence (12 - 18 years), and (viii) late adolescence (19 - 21 years) (Williams et al., 2012). These classification systems are important, especially when developing new medicines, since several biological, developmental, psychological, and social changes take place as a child grows (Williams et al., 2012). Subsequently, these changes can impact medication administration, effectiveness, and safety.

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Medications are regularly used for the treatment and prevention of several paediatric illnesses (Centers for Disease Control and Prevention, 2017). Orally dosed medications are preferred in paediatric treatment given their ease of use, dosing flexibility, and accessibility while non-oral preparations like injectable and transdermal formulations are used less frequently within this patient population due to dosing inconvenience and high variation in skin permeation respectively (Ali et al., 2014; Delgado-Charro and Guy, 2014; Thabet et al., 2018). Some commonly used oral formulations in paediatric patients include suspensions, solutions, tablets, and capsules (Ali et al., 2014; Makkawi et al., 2022; Thabet et al., 2018). Although these formulations are highly beneficial, oral liquids (e.g., solutions, suspensions) are usually poorly environmentally stable; susceptible to microbial growth; controlled by the patient or caregiver creating the potential for inaccurate dosing and; the incidences of non-compliance because large volumes are often required is common (Ivanovska et al., 2014; Lopez et al., 2015; Neves and Axtoro, 2021). Tablets and capsules on the other hand can be problematic for neonates, infants and young children who cannot or have trouble swallowing solid medications as well as for older children with dysphagia (Ali et al., 2014). The ideal oral drug delivery system for paediatrics is one that allows the drug to reach the site of action, has minimal adverse effects, and can be effectively administered to children of all ages (Nunn and Williams, 2005).

Currently, several barri ers to medication use in paediatrics exist. Approximately 30% of the paediatric medication used globally is off-label with most drug formulations approved as capsules or tablet dosage forms commonly employed as extemporaneously prepared oral solutions, for which use has not yet been approved by regulatory bodies (Allen et al., 2018; US FDA, 2018). Off-label medication use in children and adolescents can potentially lead to dosing errors and adverse effects (Huth et al., 2020). Besides, pharmacokinetics can differ greatly between the adult and paediatric populations, as well as within the different paediatric age groups. For instance, the volume of distribution varies greatly between age groups, and as a result weight-based dosing is often required for minors (Batchelor and Marriott, 2015). Additionally, an adolescent child may be able to swallow a solid tablet, whereas a neonate cannot (Ali et al., 2014). Therefore, most commercially available drug formulations are unfavourable for use in children and adolescents (Lopez et al., 2015).

One class of drug delivery systems that circumvents the complications of most oral formulations, as it relates to their use in paediatric patients are the orally disintegrating drug carriers. These are solid dosage forms designed to rapidly disintegrate within the oral cavity, usually in less than a minute, without the addition of water (Dey and Maiti, 2010; Hannan et al., 2016). The suspension/solution/dispersion that is formed in the oral cavity because of the saliva mixing with medication, can then be swallowed (Comoglu and Ozyilmaz, 2019). Compared to liquid formulations, orodispersible drug carriers are advantageous due to their smaller volume, precise dosing, and improved stability. Moreover, unlike traditional tablets and capsules, orodispersible drug formulations do not need to be swallowed whole and can be safely used in children of all ages (Ali et al., 2014). Orally disintegrating drug delivery systems are currently available as films, tablets, wafers, pellet formulations etc. (Briñak et al., 2015; Irfan et al., 2015; Costa et al., 2019).

To ensure rapid disintegration in the oral cavity, orodispersible drug carriers must have high porosity and low density. As a result, often orodispersible drug carriers are sensitive to moisture and must be stored accordingly. The taste and mouthfeel of orodispersible drug carriers is essential for their success, and sweetening agents are often required in these formulations. Super-disintegrants are also often needed to ensure rapid disintegration within the oral cavity. Differences in the manufacturing process can directly influence the properties of the orodispersible drug carriers, including the mechanical strength, disintegration rate, and friability. Examples of manufacturing methods include compression, molding, spray-drying, and sublimation (Dey and Maiti, 2010; Roy et al., 2014; Hannan et al., 2016).

The focus of this review will be on the application of orally disintegrating carriers in paediatric drug therapy. Specifically, a comprehensive analysis of current and upcoming orodispersible drug carriers and implications in the paediatric population, including recent example and innovations, have been highlighted. Given the increasing attention to orodispersible drug carriers and their potential usefulness in paediatric therapy, an up-to-date review was necessary to emphasise the several advances made in this area. By highlighting the use of these innovative drug carriers as an avenue to advance paediatric-specific drug formulations, the review serves as a resource for which further research and application of this formulation type will be developed from. As such, literature pertaining specifically to the adult population will only be used in support or when there is a lack of paediatric-specific evidence. To retrieve literature, PubMed, Embase, the Cochrane Library, and Google Scholar were searched throughout June 2022. These searches included the keywords “paediatrics”, “pediatrics”, “paediatric patients”, “children”, “adolescents”, “orodispersible drug carriers”, “orally disintegrating formulations”, “mouth dissolving drug delivery systems”, and corresponding Medical Subject Headings (MeSH) and Embase Subject Headings (EMTREE) terms, when available. English language literature published within the last five to ten years were prioritized. The best evidence was literature that directly discussed the use of orodispersible drug carriers in children and adolescents.

2. Orodispersible drug carriers

The use of medications in the paediatric population is complex, given the variability within age groups and the limited literature on the preferred routes and formulations for drug administration. While liquid dosage forms are traditionally preferred for children, there is growing interest in the use of orally administered solid dosage forms that are safe for all paediatric age groups. It is believed that solid dosage forms would avoid major disadvantages of oral liquids: poor stability, dosing inaccuracy, wastage, and non-compliance. Of special importance are solid dosage forms that can circumvent the limitations of conventional compact delivery systems, such as tablets and capsules, which is most commonly issues with swallowing and the potential for choking (European Medicines Agency, 2006). Since orodispersible dosage forms are designed to rapidly disintegrate within the oral cavity without water, they are ideal for preventing asphyxiation, especially in young children (Dey and Maiti, 2010; Hannan et al., 2016). Furthermore, the fact that water is not needed to use orodispersible preparations is key for geographical locations without access to a consistent or clean water source. Unlike oral suspensions that often require reconstitution or tablets that need water as a swallowing aid, orodispersible delivery systems can be ingested without water. Thus, they have the potential to improve paediatric treatment adherence and, ultimately, therapy effectiveness (Slavkova and Breitkreutz, 2015).

There are several classes of orodispersible drug formulations that currently exist or already being investigated, and these include orodispersible tablets, films, capsules, granules, lyophilisates/orodispersible wafers, mini-tablets, and electrospun fibers or webs. The following sections will detail these different drug delivery systems with respect to the paediatric population. Furthermore, Table 1 presents different kinds of commercialized orally disintegrating drug delivery systems for paediatric pharmacotherapy.

2.1. Orodispersible tablets

2.1.1. Overview

They are tablets intended to rapidly disintegrate in the mouth, rapidly forming a suspension or solution within 0 - 180 s. ODTs have several other designations, such as mouth-dissolving, rapid-dissolving, fast-melting, and oral disintegrating tablets. An ideal ODT requires minimal water, rapidly disintegrates in the oral cavity, has good
Although ODTs do not need to be swallowed, they should ideally be small: no larger than 8 mm. Generally, no specific limits are placed on the amount of active drug that should be loaded in orodispersible tablets, but ideally about 50 w/w % or below of the total mass of each tablet is recommended (Yapar, 2014). Drugs that have good water solubility, are not bitter in taste, and do not require a large dose are well suited for ODT formulation (Oliveira et al., 2020; Desai et al., 2022; Cornilà et al., 2022).

2.1.2. Manufacture process

To allow for quick disintegration of the ODT, the tablet must be porous; however, it is essential that it has sufficient mechanical strength to withstand packaging and handling. Thus, ODTs are manufactured to achieve a critical balance between mechanical strength and porosity. Currently, several techniques such as direct compression, sublimation,
cotton candy, phase transition processes, spray drying, mass extrusion, molding, and melt granulation are employed to produce ODTs. Also, there exist several novel patented technologies (e.g., DuraSolv®, FlashTab® etc.) in use for the development of ODTs (Badgajar and Mundada, 2011; Kumari et al., 2013; Vlad et al., 2022).

2.1.2.1. Direct compression. Direct compression involves the incorporation of the drug, often with a (super)disintegrant, in a dry state. The powder blend that is formed is then compressed into a tablet. This method of manufacturing ODTs is relatively cheap and well-established which makes it ideal for large scale production (Badgajar and Mundada, 2011; Ghourichay et al., 2021). It is preferred for drugs that are sensitive to heat or moisture (Nagar et al., 2011). Compared to other methods of preparing ODTs, fewer excipients are required, which is advantageous when designing paediatric formulations given the unknown safety of several excipients in this population. A limitation of the direct compression method is the variable and often undesirable disintegration times. However, this can be overcome by the incorporation of multiple channels which permits water to enter the ODT to enhance the disintegration process and reduce the time required (Ghourichay et al., 2021). Additionally, poor drug content uniformity is a limitation of direct compression, especially for low-dose formulations (Muselik et al., 2014). The amount of drug that can be loaded in formulations using this method is also generally limited (usually about 50 mg) (Nagar et al., 2011).

2.1.2.2. Sublimation. This process makes use of volatile substances (e.g., camphor, menthol, etc.) that are then compressed, with the excipients and drug, into a tablet. The volatile substance is removed by sublimation using high temperature and pressure making the residual bulk a highly porous tablet. Compared to direct compression, these ODTs are more porous and often disintegrate faster in the oral cavity. In addition, the evaporation of the volatile substance eliminates the use of complex processes such as the sublimation of frozen water (Bandari et al., 2008; Badgajar and Mundada, 2011; Kalyankar et al. 2015; Ghourichay et al., 2021). This method is limited by the generally costly equipment required for the sublimation process and it is not suitable for heat sensitive drugs (Nagar et al., 2011).

2.1.2.3. Cotton candy process. It employs a spinning mechanism like that used in the production of cotton candy. In this method, polysaccharides are rapidly spun and melted, forming a matrix, which is then partially recrystallized into floss-like crystals with good flow properties which allows for favourable compression during the manufacturing. The drug and excipients are then milled and incorporated into the free-flowing floss-like crystals which are then compressed to produce ODTs. Given the high heat required for this method, only non-thermolabile drugs may be used (Bandari et al., 2008; Badgajar and Mundada, 2011; Yapor, 2014). The cotton candy process is useful for taste-masking unpleasant tasting bitter drugs and allows for high doses of drugs. This method also produces ODTs with good mechanical strength which makes them easy to store (Ghourichay et al., 2021).

2.1.2.4. Phase transition process. This approach relies on the use of two different sugar alcohols. These alcohols, one with a high melting point and the other with a low one, are compressed along with the drugs and excipients into a tablet, which is then heated at a temperature between the melting points of the two alcohols. This process results in a harder tablet compared to other methods like direct compression which is helpful when it comes to drug storage and packaging (Badgajar and Mundada, 2011; Yapor, 2014).

2.1.2.5. Mass extrusion. This is based on the use of a liquid containing powder blend, usually formed from solvents such as polyethylene glycol and methanol or ethanol, acting as softeners for the drug-excipient powder mixture. The softened mass is then shaped into a cylinder, using a syringe or extruder, which can be cut into tablets using a hot blade (Kumari et al., 2013; Yapor, 2014). One potential advantage of this technique is the ability to mask the unpleasant taste of bitter drugs (Nagar et al., 2011).

2.1.2.6. Spray drying. It is used to produce a highly porous powder that can then be compressed into an ODT (Kumari et al., 2013). The process involves rapidly removing a solvent through evaporation (Kumari et al., 2013). Advantageously, ODTs made using spray drying are designed to disintegrate in the oral cavity in less than 20 s (Bandari et al., 2008; Kumari et al., 2013). However, the spray drying technique is limited by its high cost of production and yields extremely fragile ODTs which make storage challenging (Ghourichay et al., 2021).

2.1.2.7. Molding. It describes two methods for producing ODTs — Compression molding and Heat molding. In compression molding, the powder blend of drug and excipients is run through a fine screen to decrease the particle size. The powder blend is then covered or dispersed within a solvent to moisten the mixture. Finally, the mixture is compressed into a tablet shape and left to air dry, allowing the solvent to evaporate. Heat molding on the other hand involves the formation of a suspension containing water-soluble sugars and agar. Using blister packaging, the suspension is poured into the molds and the agar is left to solidify at room. The jelly that forms is then dried at 90°C using a vacuum. The result is a highly porous ODT which disintegrates in the oral cavity within 5 - 15 s. These ODTs typically have low mechanical strength and can easily be broken while handling (Badgajar and Mundada, 2011; Akdag et al., 2020; Yamada et al., 2022).

2.1.2.8. Melt granulation. It is based on the use of a meltable binder or binders with low softening point. The melted binder is used to agglomerate the excipients and drugs, and then allowed to harden at room temperature to form a waxy, solid mass. This mass is then processed inside a mixer where it melts and produces granules which are allowed to dry and then mixed with additional ingredients (if needed), sieved, and compressed into a tablet formulation. Considering the use of heat, this process can be either ideal for thermolabile compound. However, it is less time consuming than wet granulation, has no need for solvents, does not require extended drying periods, and can produce controlled release formulations (Yang et al., 2007; Kumari et al., 2013; Yapor, 2014; Ghourichay et al., 2021).

2.1.2.9. Inventions. In addition to the various techniques that are used to produce ODTs that have already been discussed, several patented technologies also exist. For instance, DuraSolv® technology was developed to produce stronger and more durable ODTs that can be packaged in bottles or blisters (Reddy et al., 2013). DuraSolv® ODTs are produced using conventional tableting equipment and are comprised of a drug, fillers, and lubricant (Kumari et al., 2013; Reddy et al., 2013). OraQuick® (KV Pharmaceuticals, Ltd.) is another example of an innovative technology used to design ODTs. OraQuick® utilizes a microsphere technology, known as a “micro mask”, as a strategy for taste-masking (Reddy et al., 2013). The ODTs produced by this method are thought to have a superior mouth feel while maintaining sufficient mechanical strength and a rapid disintegration time (Reddy et al., 2013). Ceform technology involves the preparation of drug-containing microspheres which are blended and compressed into an ODT (Kumari et al., 2013). Other unique examples include Zydis®, Wow Tab®, Pharmaburst®, Frostatech®, Advantol®, Flash Tab®.

2.1.2.10. Miscellaneous. Another growing area of manufacturing for the pharmaceutical industry is 3D printing, which has recently been applied to develop orodispersible drug carriers (Jamroz et al., 2017).
an orodispersible tablet formulation of levetiracetam intended for the treatment of partial seizures in children 4 years and older (weighing more than 20 kg), was the first US FDA approved 3D printed orodispersible drug carrier. The developers used a novel powder bed inkjet 3D printing technique to formulate the orodispersible tablets. They were designed to either disintegrate within the mouth when taken with a sip of liquid or disperse into a suspension within 15 s when placed in about 10 mL of water. Relative to conventional tablets, Spritam had a substantial drug loading capacity (approximately 65%) and was highly porous in nature — which intensely increased its surface area and dissolution/disintegration rate (Prasad and Smyth, 2015; Jacob et al., 2017; Wang et al., 2021).

It is also believed that 3D printing is beneficial for paediatric patients given the potential for personalized medicine (Eduardo et al., 2021). Eduardo and co-workers sought to determine the ideal parameters for 3D printing ODTs. To do so, the researchers developed 3D printed hydrochlorothiazide ODTs, referred to as orodispersible printlets, using semi-solid micro-extrusion 3D printing processes (Eduardo et al., 2021).

To make the orodispersible printlets, a wet mass containing hydrochlorothiazide and excipients was prepared. Simultaneously, the 3D model was created using a computer-aided design and the print parameters were set. Printing filaments were then made using micro-extrusion and the filaments were deposited into the 3D design. The authors concluded that while the optimized orodispersible printlets met the requirements set by the European Pharmacopoeia, more research is required to establish the ideal 3D printing parameters before this technique can be employed to treat patients (Eduardo et al., 2021). An apparent disadvantage of this method is the high cost required to purchase the required equipment.

2.1.3. Application in paediatric drug formulation

In addition to the several already commercially available paediatric ODTs (Table 1), there continues to be new advances. Khan et al. (2017) created atenolol and atorvastatin ODTs intending to increase paediatric treatment compliance. To make the ODTs, direct compression, sublimation, and effervescent methods were used. The commercialization of ODTs with antihypertensive effects, as in this case, helps further medication options for the paediatric population.

Similarly, Hussein and colleagues aimed to develop valsartan fast disintegrating tablets for the treatment of paediatric hypertension (Hussein et al., 2018). The valsartan ODTs were found to reduce the blood pressure of rats more rapidly than the comparative suspension. One possible explanation for the increased therapeutic efficacy of valsartan ODTs is the potential for pre-gastric drug absorption and reduced first-pass metabolism associated with orodispersible formulations. Thus, antihypertensive medications formulated as ODTs offer a possible solution for children unable to swallow conventional solid dosage forms while maintaining the same, if not better, antihypertensive effects.

Additionally, Chhajed and colleagues investigated the use of montelukast, a drug commonly used to treat asthma, as an ODT (Chhajed et al., 2012). The authors aimed to improve compliance of those unable to swallow conventional solid tablets, like children. To make the ODT, they employed the direct compression method while varying the superdisintegrant. Montelukast now exists as a commercially available ODT, known under the brand name Montair®, approved for children ages six months and older (Alipharma, 2022).

Sipos and team developed ibuprofen containing ODTs, intended for paediatric use, employing direct compression methods (Sipos et al., 2017). The authors ultimately found the optimized formulation to have ideal characteristics and as such, concluded the formulation be a suitable dosage form for paediatric patients. Ibuprofen, among other analgesics and antipyretics, are often used in children for treatment of several ailments, such as fever associated with nausea and vomiting (Bushra and Aslam, 2010; Kanabar, 2017). With that indication in mind, the availability of an ibuprofen containing ODT seems especially beneficial by minimizing the need for unfavourably tasting syrups and suspensions (Mennella et al., 2013).

2.2. Orodispersible films

2.2.1. Overview

Orodispersible films (ODFs) are single or multilayered sheets containing appropriate ingredients that rapidly disperse when placed in the mouth (Gupta et al., 2021). They are most commonly rectangles or squares; however, circles and U-Shaped ones exist (Gupta et al., 2021). They inherently have a larger surface area than ODTs and as such, often have faster disintegration time (Ozakar and Ozakar, 2021). They are also often easier to handle, and store compared to ODTs since they are generally less brittle. ODFs are used for local action in the oral cavity for disease states like ulcers or cold sores. They are also used for systemic effects to treat several disease states (Mahboob et al., 2016). Recently, Klingmann et al. compared the acceptability of ODFs compared to syrups in neonates and infants (Klingmann et al., 2020). The authors showed that ODFs are both a safe and effective dosage form for this population.

2.2.2. Manufacture process

Like ODTs, several methods currently exist for producing orally disintegrating films. These include:

2.2.2.1. Casting method. This method is commonly used due to its low cost and simplicity. The solvent casting method relies on the use of heated magnetic stirrer to prepare a viscous solution containing water soluble drug(s) and excipients. The viscous solution is first of all cast using specialized molds or petri dishes with specific dimensions and then left at room temperature over a period of time (usually 24 - 48 h) or sometimes in an oven set at 40 - 50 °C to allow evaporation of the solvents (Mahboob et al., 2016; Ozakar and Ozakar, 2021). The resulting films (with specific dimensions — diameter and thickness) can then be cut to the desired dimensions (Slavkova and Breitkreutz, 2015). Similarly, the semisolid casting method involves the creation of a viscous solution (from the drug and gel forming polymeric excipients) which is poured into specific molds, allowed to solidify into a pliable mass which can then be cut to the desired size (Mahboob et al., 2016). Generally, batch-to-batch variations in film thickness is inevitable while using this method, it requires a significantly long drying period and is not suitable for preparing films larger than 25 – 30 cm, making scale-up/large scale production problematic (Palez et al., 2022).

2.2.2.2. Extrusion. Extrusion can generally be described as either hot-melt extrusion or solid-dispersion extrusion (Mahboob et al., 2016). Using hot-melt extrusion, the drug and excipients are mixed in the dry state and heated until fluid using an extruder. (Mahboob et al., 2016; Reza and Chakraborty, 2016; Ozakar and Ozakar, 2021). The molten mixture is then expelled through the sheet-die hole while being pulled at a constant speed and wound up on a roll. Once cooled, the roll of film can then be cut to desire a length/dimensions (Richter, 2019). Solid-dispersion extrusion, on the other hand, involves the incorporation of a drug containing wet powder blend with a heated hydroalcoholic solvent. Thereafter, the resultant solid dispersion is then molded into the desired film structure. The extrusion technique allows uniform distribution of the active drugs and reduced production units thus decreasing the production steps and allowing continuity which makes it a more desirable process for large scale ODF production. However, the extrusion technique is only suitable for non-thermolabile drugs since the drug mixture needs to be heated at high temperatures (Mahboob et al., 2016; Ozakar and Ozakar, 2021). Also, it has limited value in the production of ODFs given that most polysaccharides, an important excipient in ODFs, are heat sensitive and/or can exhibit an elevated glass transition temperatures that is not usually easy to adjust with the inclusion of plasticizers, thus resulting in the formation of very sticky or ductile films.
approach, without external air currents or heat on the film surface. Post determined amount of this master batch is then transferred onto a roller
mers, other excipients, and solvents are combined to form a solution or
(Musazzi et al., 2020; Palezi et al., 2022) E.A. Kean and O.A. Adeleke
drying, the ODF is formed which are then cut to the desired sizes, shapes,

2.2.2.4. Printing technologies. A more recent approach to formulating ODFs involves the use of two-dimensional (2D) or three-dimensional
(3D) printing technology for formulating drug-containing ODFs (Oblom et al., 2019). Briefly, the process involves first preparing a polymer/excipient blend without the active drug which is generally used later as the substrate for printing the drug containing solution or suspension with a printer. Films are usually printed one at a time, and left to dry overnight (Oblom et al., 2019; Palezi et al., 2022). Since this approach involves the delayed deposition of the active drug on the excipient substrate using the printer, this helps preserve the drug from thermal or mechanical degradative stress associated with the production and drying phases. This technique can be used for preparing polymeric matrices that are useful for the encapsulation of precise amounts of drugs/bioactive agents and, production can be done on demand, thus offering a unique way of making ODFs for individualized therapy. Printing technologies are limited by the high costs and time required, often leading to only small quantities being prepared per time (Musazzi et al., 2020; Palezi et al., 2022).

2.2.3. Application in paediatric drug formulation

There are currently several research groups working on developing ODFs with the paediatric population in mind. Senta-Loys et al. sought to design tetrabenazine ODFs for the treatment of hyperkinetic movement disorders in paediatrics (Senta-Loys et al., 2017). Before this effort, no paediatric-approved drug form of tetrabenazine existed so crushed tablets were used. They prepared the tetrabenazine ODFs using the casting/evaporation method. To do so, a gel, containing a film-forming polymer, excipients, and tetrabenazine, was cast onto a petri dish and dried. The final step involved cutting the films such the final product had a surface area of 4 cm².

Additionally, Preis et al. designed ODFs of dimenhydrinate, for use in paediatrics, as an alternative to its marketed formulations — tablets, syrups, and suppositories. The researchers determined the disintegration time of the dimenhydrinate ODFs to be between below one minute and below 2 min for the petri dish and drop method, respectively (Preis and Breitkreutz, 2012).

Due to the shortage of paediatric-specific tuberculosis drug formulations, Matawo et al. designed pyrazinamide containing ODFs for the treatment of tuberculosis in children (Matawo et al., 2020). Using the solvent casting method, the pyrazinamide ODF was prepared with varying amounts of excipients. The optimized ODF was found to disintegrate in less than 60 s in addition to being flexible, thin, and easy to handle. The authors concluded that the developed formulation offered a potential solution to the several current challenges preventing the successful treatment of tuberculosis in the paediatric population.

Despite warfarin, a narrow therapeutic index drug, being used in several instances to prevent thrombotic events in paediatrics, there are currently no available paediatric-specific drug formulations (Oblom et al., 2019). Oblom and co-workers aimed to investigate the issue by comparing the traditional dosage form, oral powders in unit dose sachets (OPSs), to ODFs. In terms of dose uniformity, the prepared ODFs were found to be superior to the conventional OPSs. Interestingly, the authors were able to print QR codes on the ODFs using edible ink; the QR codes could be used to avoid medication errors. The authors reported the use of warfarin containing ODFs prepared by printing methods would be advantageous, especially in hospital settings, by offering personalized medicine to the paediatric population.

Knowing that often drug formulations require more than one API, Thabet et al. (2018b) aimed to produce a multi-layered ODF containing both enalapril and hydrochlorothiazide. The researchers used the solvent casting method to prepare the multi-layer ODF; it was found that using different polymers between the film layers decreased the migration of the APIs between the layers. The production of multi-drug-containing formulations offers several possible advantages in the paediatric population, including increased compliance and therapy effectiveness.

ODFs can be prepared using hot-melt extrusion, but this technique is limited by the hot temperatures required which often results in the exclusion of thermosensitive drugs (Khalid et al., 2021). To investigate hot-melt extrusion, Khalid et al. (2021) used diclofenac sodium, a thermosensitive drug, to prepare ODFs intended for the paediatric population. The preparation involved leaving the diclofenac-containing paste in a heated chamber at 95°C for 10 min so the melted mixture could be printed and packaged. The authors concluded the hot-melt extrusion was a useful method to prepare diclofenac ODFs and could likely be applied to other thermosensitive drugs.

2.3. Orodispersible lyophilisates/wafers

2.3.1. Overview

Orodispersible lyophilisates (ORLs), also known as orodispersible wafers (ORWs), are produced from a solution or suspension containing the additives and APIs and then freeze-dried directly in the blister package. They are a highly porous solid dosage forms with diverse dimensions depending on the type of casting mold employed and commonly require special peel-off blister packaging because they are very fragile. This can be disadvantageous for patients with visual or motor impairment, however, this type of packaging can also prevent young children from accessing the medication unsupervised which could be considered an advantage. Additionally, ORLs have low mechanical strength and poor stability at higher temperatures and humidity (Bandari et al., 2008; Costa et al., 2019; Noshi et al., 2022).

2.3.2. Manufacture process

Orodispersible lyophilisates, also called orodispersible wafers, are produced by lyophilization (i.e., freeze drying). It is the process whereby a solvent is removed from a given solution or suspension, containing structure-forming additives, resulting in a highly porous and lightweight product (Bandari et al., 2008). An example of a commercially available product that follows this process is Zofran Zydis®, which is approved for children older than six months for nausea and vomiting. Zofran Zydis is produced by dispersing ondansetron in a matrix made of polymers and saccharides. The mixture is then transferred into blister packaging and then rapidly frozen using liquid nitrogen. Lyophilization occurs and the ice crystals produced during the freezing process are sublimed (Douroumis, 2010; Slavkova and Breitkreutz, 2015). The resulting product is a highly porous and friable ORL. Unfortunately, the production of ORLs often requires expensive equipment and can be quite time-consuming (Wiedey et al., 2021).

2.3.3. Application in paediatric drug formulation

Deng et al. recently investigated the use of nanoparticle-based oro-dispersible drug carriers, using nanoprecipitation and lyophilization, with the goal of improving the taste and bioavailability of paediatric drugs (Deng et al., 2021). To test this idea, the researchers used lopinavir and ritonavir to exemplify unpleasant-tasting drugs. The authors
concluded that the method of preparation demonstrated to be a promising way to overcome unpleasant tasting drugs. Another instance of how ODWs were utilized in the paediatric population is when Kerrison and team investigated the use of zolmitriptan ODWs for the treatment of childhood migraines (Kerrison et al., 2014). The researchers conducted a prospective audit and found the 71.4% of paediatric patients had symptomatic relief and minimal side effects after using the zolmitriptan ODWs. The researchers were the first to demonstrate the potential benefit for zolmitriptan ODWs in the paediatric patient.

Owing to the lack of current paediatric appropriate anti-human immunodeficiency virus drugs, Lal and colleagues sought to develop lopinavir and ritonavir containing ORLs (Lal et al., 2017). The freeze-drying technique in conjunction with child-safe excipients were used to prepare the ORLs. The prepared ORLs were satisfactory as they disintegrated in less than 10 s, were easy to remove from the blisters, and physical properties remained similar after storing them for three months. The authors concluded that the availability of paediatric-specific anti-retroviral dosage forms would be of great benefit, especially in low-resource settings.

2.4. Orodispersible capsules

2.4.1. Overview
Orodispersible capsules (ODCs), also referred to as fast disintegrating capsules, are modified conventional hard gelatin capsules with brittle shells (Aboul-Einien et al., 2009). Though not frequently explored, they are believed to minimize several of the disadvantages of ODTs like low physical resistance, low drug loading, and high friability (Aboul-Einien et al., 2009).

2.4.2. Production and application in paediatric drug formulation
Aboul-Einien et al. developed an ODC of meloxicam with the goal of increasing the bioavailability of the medication (Aboul-Einien et al., 2009). To do so, the meloxicam was mixed with excipients to form a homogenous blend, the blend was titrated with water forming a paste, left to dry at room temperature, and finally, freeze-dried producing the filling mixture. The brittle capsule shells were then prepared using size one hard gelatin capsules that were equilibrated, frozen, and lyophilized. Finally, the ODCs were assembled by filling the freeze-dried capsule shells with the filling mixture. The disintegration time of the ODCs was determined to be 23 s and volunteers reported the ODCs to have a pleasant mouth feel. The availability of meloxicam, a non-steroidal anti-inflammatory drug, as an ODC is beneficial in the paediatric patient, when prescribed, especially during times of illness when oral liquids may be hard to consume.

Similarly, Ciper and collaborators designed fast disintegrating capsules with conventional hard capsules using perforation and vacuum-drying techniques (Ciper and Bodmeier, 2006). Using the perforation method, conventional hard capsules were perforated with a needle with a varying number of holes (two, six and ten). On the other hand, the vacuum-dried capsules were made by taking the equilibrated hard gelatin capsules and drying them in a vacuum oven. The ODCs were found to have a high drug loading capacity, especially when compared to other types of oro-dispersible drug carriers like ODTs.

2.5. Orodispersible granules and pellets

2.5.1. Overview
Orodispersible granules (ODGs) and pellets (ODPs) are multiparticulate dosage forms where the dose of a drug is distributed into multiple small-size carriers. Unlike conventional granules which are compressed into tablets, used to fill capsules, or mixed to form a suspension or solution, ODGs can be administered directly into the oral cavity. Additionally, they can be mixed with a drink or soft food before administration, which may help mask the taste of unpleasant drugs. One challenge associated with ODGs is the need for sufficient taste-masking given that ODGs remain in the mouth longer than tablets (Slavkova and Breitkreutz, 2015; Disch et al., 2016; Cornila et al., 2022).

2.5.2. Manufacture process
They are manufactured largely using the same processes as conventional granules and pellets, respectively (Slavkova and Breitkreutz, 2015). Both granulation and palletisation techniques can be used to produce ODGs (Teran, 2016). While wet and dry granulation techniques can both be used, Kawano and team used wet granulation to prepare furosemide ODGs (Kawano et al., 2010). These ODGs were prepared by mixing furosemide with yogurt powder and an aqueous solution of maltitol which functioned as taste-masking agents. Subsequently, the produced granules were engineered into a compact delivery system utilizing microcrystalline cellulose and mannitol as binders. The oro-dispersible matrix generated was left to dry over twenty-three h, passed through a sieve to streamline particle size distribution. Besides, Taj and colleagues prepared oro-dispersible pellets using the extrusion coupled with spheronization methods which also aided masking of the unpleasant-tasting drugs ambroxol and cetirizine. The optimized ODP developed using this approach was found to disintegrate in the buccal environment in less than 20 s using human subjects (Taj et al., 2014).

2.5.3. Application in paediatric drug formulation
Acetaminophen was developed as a fast-disintegrating pellets for use in paediatrics employing the extrusion/spheronization and freeze-drying methods. The process was successful, resulting in a multi-particulate dosage form with high drug loading capacity, low friability, and instantaneous disintegration within 5 s. The authors concluded that the ODGs offer a valuable solution to administration and dosing challenges in paediatrics (Thi et al., 2015).

2.6. Orodispersible mini-tablets

2.6.1. Overview
Orodispersible mini-tablets (ODMTs) are solid dosage forms generally with a diameter of 2 - 4 mm, a surface-to-volume ratio of at least 2 mm⁻¹, and an aspect ratio of approximately one (Comoglu and Ozylmaz, 2019; Lura et al., 2021). In addition to these characteristics, ODMTs also have the distinguishing feature of all oro-dispersible drug carriers whereby they disintegrate in the oral cavity in 30 - 180 s. Compared to ODTs, the small size of ODMTs increases the acceptability of the dosage form in the paediatric patients. ODMTs with diameters between 2 - 3 mm diameters have been shown to be suitable for children who are six months to eight years of age, respectively. ODMTs are useful for infants and toddlers requiring weight-based dosing due to the high dosing flexibility of the dosage form. One limitation of ODMTs is the very limited drug loading capacity, often resulting in the patient being required to take multiple ODMTs (El-Say et al., 2015; Comoglu and Ozylmaz, 2019; Lura et al., 2019; Wiedey et al., 2021).

2.6.2. Manufacture process
The manufacturing process of ODMTs is largely the same as ODTs, including direct compression and granulation (Soulairol et al., 2018; Kokott et al., 2021). Stoltenberg et al. was of one of the first groups to construct ODMTs with the paediatric population in mind (Stoltenberg and Breitkreutz, 2011). To prepare the ODMTs, hydrochlorothiazide and five commercially available excipients, that contained mannitol as the main component, were used. Using direct compression, the various powder mixtures were compressed into biconvex mini-tablets with a diameter of 2 mm.

2.6.3. Application in paediatric drug formulation
Currently, there are no commercially available ODMTs on the market, but several projects are in the works (Slavkova and Breitkreutz, 2015; Khan et al., 2021). El-Say et al. worked to develop risperidone ODMTs for paediatric use (El-Say et al., 2015). They used direct
compression to prepare risperidone 5 mg ODMTs with a 2 mm diameter. Using statistical optimization, the researchers deemed the ODMTs to be a successful formulation based on having sufficient mechanical strength, uniformity of mass, a rapid disintegration time, and minimal friability. Another instance of ODMTs being developed for paediatric use is with enalapril maleate for the treatment of hypertension (Ortega et al., 2020). Hypertension is a serious condition in paediatrics, consequently, children-specific drug formulations are necessary. Ortega and team successfully designed an optimal ODMT formulation containing enalapril maleate as a drug model using varying lactose co-pressed excipients by direct compression (Ortega et al., 2020). The enalapril maleate loaded ODMT was completely disintegrated within 28 s and considered suitable for further development and manufacturing.

2.7. Orodispersible electrospun fibers and webs

2.7.1. Overview
Electrospinning is a newer advancement in the development of orodispensible drug carriers. The process starts by generating a high electrical field which is used to form a charged jet of polymer solution. (Illangakoon et al., 2014; Nagy et al., 2010). The solvent evaporates in the air, leaving behind a charged fiber that is retrieved on a metal screen (Illangakoon et al., 2014). The result of the process is solid nanofibers, which subsequently can be formed into an orally dissolving web (ODW) (Nagy et al., 2010). It is believed that this technology has enormous potential in the development of orodispensible drug carriers owing to the large surface area created in the process (Nagy et al., 2010). Importantly, the electrospinning technique allows for two or more APIs to be easily incorporated (Illangakoon et al., 2014).

2.7.2. Manufacture process
The resulting electrospun fibers and webs produced using electrospinning can be utilized to produce ODFs. Chachlioutaki and co-workers sought to develop ODFs of isoniazid for the treatment of paediatric tuberculosis using electrospinning techniques (Chachlioutaki et al., 2020). To do so, an aqueous solution of semi-synthetic and natural polymers was pumped at a flow rate of 0.5 mL/hour while a voltage of 20 kV was administered. Using aluminium foil, the resulting electrospun mats were collected. The optimized ODF disintegrated in less than 15 s of contacting salivary fluid and total drug release occurred in less than 60 s. Development of orodispensible drug carriers containing drugs that can be used in low resource settings, in this case isoniazid to treat tuberculosis, can help ensure adherence and effective treatment. Advantages of electrospinning include good mechanical properties and fast disintegration time of the manufactured orodispensible drug carrier (Lyszczarz et al., 2021). On the other hand, the stability of orodispensible electrospun fibers may be a limiting factor. Lyszczarz and colleagues formulated electrospun aripiprazole and found the mechanical properties of the formulation worsened over time and drug recrystallizing occurred (Lyszczarz et al., 2021).

2.7.3. Application in paediatric drug formulation
There is currently very limited research on the use of orodispensible electrospun fibers and webs in both the paediatric and adult populations. One of the very few examples was the work done by Illangakoon and colleagues that developed electrospun fiber-containing paracetamol and caffeine for use in pediatrics. The nanofibers fabricated had an average diameter of 400-1600 nm and disintegrated within 0.5 s. The authors concluded that the fibers developed offered a useful drug delivery opportunity for the paediatric population (Illangakoon et al., 2014).

Rustemkyzy and colleagues (2015) aimed to address iodine deficiency in paediatric patients by developing a child-friendly, ultrarapidly dissolving orodispensible films containing iodine as a supplement. The researchers used the electrospinning technique to construct an iodine-containing nanofiber-based ODF. The prepared dosage form disintegrated rapidly and is thought to provide a potential solution to iodine deficiency in children.

3. Choice of excipients
The use of excipients is what transforms that drug or API into the desired orodispensible drug formulation. While the API itself plays a role in the choice of excipients, the target population, clinical condition, and desired pharmacokinetics must all be considered (Panda et al., 2015). In addition, the use of excipients in the paediatric population must also be well-thought-out to ensure safe and non-toxic formulations (Thabet et al., 2018). In all instances, the excipients’ benefits must be weighed against their potential risks. It is recommended the following sources be consulted in the stated order to assess the safety of excipients prior to use in paediatric drug formulations: International Harmonization Conference (ICH) or European Medicines Agency (EMA) guidelines; Committee for Medicinal Products for Human Use (CHMP) opinion; current authorized paediatric medicines; European food legislation; European Food Safety Scientific (EFSA) opinions; other sources including toxicological, pre-clinical, or clinical data (European Medicines Agency, 2013). Table 2 summarizes the excipients classes commonly used in orodispensible drug delivery.

3.1. Superdisintegrants
They usually play an important role in the mechanism of orodispensible drug delivery systems. Superdisintegrants are added to control the rate of disintegration. Typically, superdisintegrants account for 10-20% and 0-8% of the formulation weight in ODTs and ODFs, respectively (Panda et al., 2015; Ghourichay et al., 2021; Ozakar and Ozakar, 2021). Several aspects can influence the rate of disintegration including the amount of superdisintegrant, the percentage of superdisintegrant relative to the rest of the formulation, and the method use to add the superdisintegrant (Reshma and Senthila, 2020). Superdisintegrants aid in the disintegration due to swelling, wicking, repulsive forces and/or deformation mechanisms (European Medicines Agency, 2013). For example, when Dad and colleagues (2021) developed fluoxetine orodispensible films intended for paediatric patients, crospovidone was used as the superdisintegrant and the resulting ODFs had a disintegration time of under 30 s and achieved complete drug release within 3 min. Furthermore, Redai and group explored delivering fluoxetine by utilizing a polymer-based, fast dissolving film technology (as an alternative delivery system to commercially available oral solution, capsule, and tablet) for addressing the issues of non-adherence in paediatric patients. These films were fabricated using the solvent casting method, had a disintegration time of below 2 min and released approximately 100% fluoxetine within 15 min (Dezena and Tardim, 2022).

3.2. Fillers and matrix formers
Several classes of excipients are beneficial during the manufacturing of orodispensible drug carriers, specifically ODTs and ODMTs. Fillers, also known as diluents, are a group of excipients that are capable of influencing the bulk, disintegration rate, and mechanism of drug release of orodispensible delivery systems (Panda et al., 2015). Ibrahim et al. studied the effects of various fillers, including mannitol, spray-dried lactose, and sorbitol, on the formulation properties of valsartan ODTs (Ibrahim and El-Setouhy, 2010). The researchers found that ODTs formulated with mannitol or spray-dried lactose had favourable properties, unlike ODTs containing sorbitol, which were sticky, friable and difficult to remove from blister packaging (Ibrahim and El-Setouhy, 2010). The choice of filler in the paediatric population must be thoroughly investigated due to the potential for unwanted side effects in paediatric patients (Belayneh et al., 2022). For example, lactose and mannitol have been reported to cause hypersensitivity reactions, abdominal pain, and diarrhea in paediatrics (Belayneh et al., 2022;
Table 2

<table>
<thead>
<tr>
<th>Excipients Class</th>
<th>Purpose</th>
<th>Examples</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiadhesives</td>
<td>Prevent adhesion of the drug mixture to the punches/walls</td>
<td>Talc, corn starch</td>
<td>(Panda et al., 2015)</td>
</tr>
<tr>
<td>Colouring agents</td>
<td>Determines the colour of a given pharmaceutical product</td>
<td>Brilliant blue FCF, Fast green FCF, Orange II</td>
<td>(Panda et al., 2015)</td>
</tr>
<tr>
<td>Fillers/Diluents</td>
<td>Increase bulk, impact the disintegration rate, and mechanism of drug release</td>
<td>Mannitol, sorbitol, calcium carbonate, lactose</td>
<td>(Ibrahim and El-Setouhy, 2015; Panda et al., 2015)</td>
</tr>
<tr>
<td>Film Formers</td>
<td>Influence disintegration, strength, and shape of ODFs</td>
<td>Pectin, gelatin, maltodextrins, HPMC E-3 and K-3, Eudragit</td>
<td>(Arya et al., 2015; Ozakar and Ozakar, 2021)</td>
</tr>
<tr>
<td>Flavouring agents</td>
<td>Establishes the taste (often smell) of the pharmaceutical formulation</td>
<td>Wild cherry, lemon, orange, bitter, peppermint</td>
<td>(Panda et al., 2015)</td>
</tr>
<tr>
<td>Gildants</td>
<td>Reduce interparticle friction</td>
<td>Corn starch, colloidal silica</td>
<td>(Panda et al., 2015)</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Improve flow of granules and prevent sticking of materials</td>
<td>Stearic acid, magnesium stearate, zinc, calcium, talc, polyethylene glycol</td>
<td>(Panda et al., 2015)</td>
</tr>
<tr>
<td>Matrix formers</td>
<td>Increase matrix strength and formulation bulk</td>
<td>Kollidon® SR, gelatin, xanthan gum, aerosol, sodium alginate</td>
<td>(Adeleke et al., 2018; El-Refai et al., 2018; Mahajan and Kelkar, 2017; Noshi et al., 2022)</td>
</tr>
<tr>
<td>Plasticizers</td>
<td>Increase the flexibility of ODFs</td>
<td>Glycerin, malic acid, sorbitol, castor oil</td>
<td>(Utazak and Ozakar, 2021)</td>
</tr>
<tr>
<td>Saliva Stimulants</td>
<td>Increase production of Saliva</td>
<td>Malic acid, ascorbic acid, lactic acid, citric acid</td>
<td>(Duix and Puthli, 2009; Hofmann et al., 2011; Wasilewska and Winnicka, 2019)</td>
</tr>
<tr>
<td>Superdisintegrants</td>
<td>Control the rate of disintegration</td>
<td>Aegle marmelos gum, croscarmellose sodium, sodium alginate, crospovidone</td>
<td>(GhouriChay et al., 2021; European Medicines Agency, 2013; Panda et al., 2015)</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Acts as a solubilizing, wetting, or dispersing agent</td>
<td>Sodium lauryl sulfate, benzalkonium chloride, tweenes</td>
<td>(Arya et al., 2015; Wasilewska and Winnicka, 2019)</td>
</tr>
<tr>
<td>Sweeteners</td>
<td>Used to mask the taste of unfavourable tasting drugs</td>
<td>Sucrose, fructose, aspartame, sorbitol</td>
<td>(Panda et al., 2015)</td>
</tr>
</tbody>
</table>

Matrix formers are used in orodispersible drug formulations to increase matrix strength and add bulk (Mahajan and Kelkar, 2017). While developing ODTs, El-Refai et al. used gelatin, xanthan gum, sodium alginate, and aerosol as matrix formers (El-Refai et al., 2018). The researchers found ODTs containing gelatin had the shortest disintegration time while xanthan gum had the longest; however, statistically there was no significant difference (El-Refai et al., 2018). Similarly, Noshi and colleagues (2022) found using gelatin as the matrix former resulted in a shorter wetting time and faster disintegration than sodium alginate, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethyl cellulose containing ODTs.

3.3. Lubricants

Lubricants are used in solid tablet formulations, like ODTs, to improve the flow of granules and prevent sticking of materials during the manufacturing process. Examples of lubricants commonly used in orodispersible formulations include stearic acid, magnesium stearate, and zinc (Panda et al., 2015). For example, Laura et al. used magnesium stearate and sodium-stearyl fumarate as lubricants to prevent the ODMTs from sticking to the punches and dies (Laura et al., 2019). Additionally, Sharma et al. developed ambroxol ODTs, intended for paediatric use, using sodium stearyl fumarate as the lubricant (Sharma et al., 2014). Compared to the lubricant magnesium stearate, sodium stearyl fumarate resulted in reduced metallic taste while maintaining sufficient compressibility features (Sharma et al., 2014).

3.4. Glidants and antiadhesives

Glidants are added to solid drug formulations to reduce interparticle friction and improve flow during the manufacturing process while antiadhesives prevent the powder from sticking to the face of the punches and die walls during the production process. Examples of commonly used glidants and antiadhesives include corn starch, colloidal silica, and talc (Panda et al., 2015). In the preparation of antacid ODTs using direct compression, Gandh et al. used magnesium stearate and talc as glidants (Gandh et al., 2011). In this case, the magnesium stearate and talc prevented the tablets from sticking to the 12 mm flat faced punches the researcher used to compress the tablets (Gandh et al., 2011).

3.5. Organoleptic property modifiers

Organoleptic properties include the colour, taste, smell, and shape of the orodispersible drug carrier. These properties impact the appearance of the drug formulation and thus, play a crucial role in the acceptability and adherence of the drug. Colourants, flavouring agents, and sweeteners are examples of excipients that impact the organoleptic properties of a medication. Colouring agents are known as substances used to regulate the colour of a given pharmaceutical formulation and can be classified as water-soluble dyes and lake pigments. Generally, they are to be avoided in paediatric dosage forms due to potential complications like anaphylactic reactions, asthma, angioedema, and hyperkinesis. Use of colouring agents in orodispersible drug carriers for reasons like patient acceptability or medication error prevention must be justified alongside the potential risks. Flavouring agents are added to give the formulation a desired taste and smell. Like colouring agents, flavouring agents can be divided into several classes including natural and artificial (European Medicines Agency, 2013; Panda et al., 2015; Belayneh et al., 2022). Of the several available flavouring agents, peppermint oil should be avoided in paediatric population due to potential complications like muscle pain and burning sensations (Belayneh et al., 2022). Lastly, sweeteners are a group of excipients used in orodispersible preparations to mask the taste of bitter drugs and improve palatability in general (GhouriChay et al., 2021; Panda et al., 2015; Wiedey et al., 2021). The use of sweeteners in paediatric dosage forms must be carefully considered as there are risks associated with them. For example, the use of sucrose, fructose, and sorbitol is not recommended in children due to potential safety concerns like dental caries, laxative effects, and abdominal pain respectively (Belayneh et al., 2022).

3.6. Film formers

In the production of orally disintegrating systems, particularly films, one excipient class that is essential is film formers. Film formers...
typically account for 40-50% of an ODFs weight. Most often, film formers are water soluble polymers including HPMC E-3 and K-3, pullulan, pectin, and gelatin. Film formers are used in ODFs to ensure rapid disintegration, sufficient mechanical strength, and to hold a desired shape. The film former used should be non-toxic and have adequate wetting and spreading properties. The choice of film forming agent largely determines the properties of the final ODF, including transparency, dispersion time, and thickness. Gelatin can be used to produce glossy ODFs, whereas pullulan can be used to produce thin ODFs with high mechanical strength. Additionally, film formers can be combined to achieve desired ODFs properties (Arya et al., 2010; Wasilewska and Winnicka, 2019; Ozakar and Ozakar, 2021).

3.7. Plasticizers

Another excipient class commonly used in ODFs is plasticizers. Plasticizers are used to increase the flexibility and decrease the friability of ODFs. Tensile strength and elongation properties of ODFs are enhanced by the addition of plasticizers. Plasticizers typically account for 0-20% w/w of the formulation weight. Inappropriate amounts of plasticizers may result in cracking and splitting of the ODF along with impaired absorption of the drug. Examples of plasticizers include glycerin and castor oil (Dixit and Puthli, 2009; Arya et al., 2010; Ozakar and Ozakar, 2021).

3.8. Saliva stimulants

Saliva stimulants are a class of excipients used to increase the production of saliva. By increasing the amount of saliva in the oral cavity, these agents often act to increase the rate of disintegration. Saliva stimulants are often acidic in nature (e.g., citric acid and malic acids); however, sugars (e.g., glucose and fructose) can also act as saliva stimulants (Dixit and Puthli, 2009; Hoffmann et al., 2011; Wasilewska and Winnicka, 2019).

3.9. Surfactants

Surfactants are used as solubilizing, wetting, or dispersing agents in orodispersible drug formulations (Arya et al., 2010; Wasilewska and Winnicka, 2019). Consequently, upon contact with saliva, surfactants can assist in the disintegration of the formulation (Wasilewska and Winnicka, 2019). Examples of surfactants commonly used orodispersible formulations include benzalkonium chloride, sodium lauryl sulfate, and bezthonium chloride (Arya et al., 2010; Wasilewska and Winnicka, 2019).

4. Quality control

Orodispersible carriers, like all drug dosage forms, must follow certain standards to ensure a consistent and optimal drug delivery. Ideally, these formulations should require minimal water to disintegrate, have sufficient mechanical strength to withstand handling, and have a high drug loading capacity (Ghourichay et al., 2021; Hirani et al., 2009). Due to the high porosity and hygroscopic properties of most orodispersible systems, they often must be stored using peel-off blister packaging since they cannot be kept under normal temperature and humidity conditions (Hirani et al., 2009). When developing orally disintegrating formulations, it is important to test and measure key physicochemical and physicomechanical properties to ascertain their quality. Our discussions on quality control will mainly focus on the more commonly applied categories, namely the orally disintegrating tablets, mini-tablets, and films; however, these strategies can be applied to other orodispersible dosage forms. It is important to note that while similar testing criteria have been described to investigate several of these parameters, including disintegration, of uncoated or plain-coated tablets by the United States Pharmacopeial Convention (USP) and the European pharmacopeia (Ph Eur), no specific test criteria have been designed, as of yet, for orally disintegrating drug carriers (even the most commonly applied ones — tablets and films) (Cornilia et al., 2022; United States Pharmacopeia, 2022). Specifics regulations on disintegration testing for ODTs can be found in the 2008 Guidance for Industry, Orally Disintegrating Tablets, provided by the FDA (Center for Drug Evaluation and Research 2008).

4.1. Quality control of ODTs and ODMTs

4.1.1. Wetting time

It is defined as how long it takes for a tablet to become moist (Ghourichay et al., 2021; Hirani et al., 2009). This measurement directly influences the disintegration time of a tablet, and as such, a low wetting time is desired for a rapid disintegration time (Ghourichay et al., 2021; Hirani et al., 2009). Srivastava et al. recorded wetting periods by placing their ODT on tissue paper in a petri dish filled with water (Srivastava et al., 2010). They then measured the time it took for the water to reach the upper surface of the ODT. The test was completed multiple times, and the mean and standard deviation were calculated.

4.1.2. Disintegration time

As mentioned earlier, ODTs should disintegrate in no more than 180 s (Ph Eur) (Hellberg et al., 2021) and preferably in less than 30 s (USP) (Abay and Ugurlu, 2015). One way to determine the disintegration time is to use a basket sinker (Hirani et al., 2009). This method consists of a basket sinker filled with ODTs, which is then submerged in water and rotated at 100 rpm at 37°C. The time required for the tablet to completely fragment and pass through a screen is recorded as the disintegration time.

4.1.3. Dissolution test

The dissolution test measures the release rate of the API in an ODT (Ghourichay et al., 2021; Hirani et al., 2009). This test can be conducted for ODTs using the same methods as for conventional tablets. In particular, one can perform dissolution tests for ODTs using a basket (USP 1), a paddle (USP 2), or a flow-through cell (USP 4) (United States Pharmacopeial Convention, 2022). Most commonly, a paddle apparatus set at 50 rpm is used for ODTs. Khan and co-workers used a paddle apparatus with a phosphate buffer of pH 6.8 as their dissolution media in the development of their atenolol ODT (Khan et al., 2017).

4.1.4. Organoleptic properties

Organoleptic properties include colour, odour, and taste. The physical appearance of ODTs, including size, colour, surface texture, and identification markings, should be consistent (Shyamnipanikar and Vikharoddinkadri, 2021). Most commonly, the physical appearance is observed using visual inspection. To evaluate the taste of an ODT, a taste assessment, using human volunteers and a scoring system, can be employed (Noorjahan et al., 2014). Organoleptic properties can heavily impact patient acceptability, so they should be carefully considered (Shyamnipanikar and Vikharoddinkadri, 2021).

4.1.5. Tablet thickness

To test tablet thickness, ten ODTs should be selected at random, and their diameter and thickness should be measured (Shyamnipanikar and Vikharoddinkadri, 2021). Thickness is recorded in mm and can be measured using vernier callipers (Shyamnipanikar and Vikharoddinkadri, 2021). Tablet thickness is an important property to consider for patient acceptability, packaging, and storage.

4.1.6. Weight variation

The weight of twenty ODTs should be recorded and averaged. To have an acceptable drug formulation, the weight of the ODTs must be consistent (Shyamnipanikar and Vikharoddinkadri, 2021).
4.1.7. Hardness

Hardness measures the amount of force required to break a tablet, and is a representation of its mechanical integrity (Bhowmik et al., 2009; Hirani et al., 2009). Although ODTs are generally softer than regular immediate-release tablets, they must be hard enough to withstand packaging and handling (Hirani et al., 2009). The hardness of ODTs can be measured using conventional methods like with a hardness tester (Bera and Mukherjee, 2013). Hardness is most often expressed as kg/cm² (Bera and Mukherjee, 2013).

4.1.8. Friability

The friability of an ODT, which is an indicator of the mechanical strength, can be determined by using a friabilator (Shyamnipsanikar and Vikharoddinkadri, 2021). One way to conduct this test, is by placing a pre-weighed ODT in a friabilator set to 25 rpm for 4 min (Comoglu and Ozyilmaz, 2019; Shyamnipsanikar and Vikharoddinkadri, 2021). The ODT is then reweighed and the loss in weight, which corresponds with friability, is expressed as a percentage (Shyamnipsanikar and Vikharoddinkadri, 2021). As stated in the United States Pharmacopeia (USP), the friability should ideally be less than 1% (Ghourichay et al., 2021).

4.1.9. Moisture uptake

Due to the production and hygroscopic excipients used in ODTs, they are often moisture-sensitive (Ghourichay et al., 2021; Hirani et al., 2009). To measure moisture uptake, ten tablets should be weighed and placed in a desiccator at 75% relative humidity (Comoglu and Ozyilmaz, 2019; Ghourichay et al., 2021). After fifteen days, the increase in weight is recorded (Comoglu and Ozyilmaz, 2019; Ghourichay et al., 2021). This test determines the stability of the ODT in the presence of moisture, which will influence how the it must be packaged and stored (Ghourichay et al., 2021).

4.1.10. Content uniformity

Content uniformity is an important property that estimates the quantity of active ingredient(s) contained in an individual orodispersible formulation. The test can be performed by randomly selecting twenty formulations, which are then individually powdered and dissolved in a solvent system (Ghourichay et al., 2021; Irfan et al., 2015). Using an ultraviolet spectrophotometer or any other quantification method, the absorbance of the API is measured at a specified wavelength and a calibration curve is used to calculate the concentration (Visser et al., 2015). To be considered acceptable, the content should be within 85-115% of the specified value (Irfan et al., 2015).  

4.2. Quality control of ODFs

Like ODTs and ODMTs, ODFs should have several factors tested including disintegration and dissolution times, content uniformity, moisture uptake, and thickness (Irfan et al., 2015; Visser et al., 2015; Wasilewska and Winnicka, 2019). In addition to these factors, ODFs must also be tested for tensile strength, tear resistance, folding endurance, young’s modulus, percent elongation, moisture content, surface pH, dryness/tack test, swelling, and transparency.

4.2.1. Tensile strength

Tensile strength is a measure of mechanical robustness and is representative of the maximum force required to stretch/break the film (Visser et al., 2015; Wasilewska and Winnicka, 2019). To measure tensile strength, a minimum of six ODFs are secured between two clamps and pulled (Visser et al., 2015; Wasilewska and Winnicka, 2019).

4.2.2. Tear resistance

The ability of an ODF to withstand rupturing is denoted as tear resistance (Irfan et al., 2015; Wasilewska and Winnicka, 2019). The magnitude of force required to tear the film can be determined by placing the ODF between two sturdy holders and applying force until the ODF breaks apart (Irfan et al., 2015; Wasilewska and Winnicka, 2019).

4.2.3. Percent elongation

Percent elongation is a measure of a films ability to stretch without being damaged upon the exertion of stress (Irfan et al., 2015; Wasilewska and Winnicka, 2019). Percent elongation, also referred to as strain, can be calculated by dividing the change in film length by the initial length (Irfan et al., 2015). Typically, increasing the amount of plasticizer in an ODF results in increased elongation (Irfan et al., 2015; Wasilewska and Winnicka, 2019).

4.2.4. Young’s modulus

Young’s modulus, also referred to as elastic modulus, is used to determine film stiffness and relates to an ODFs hardness and brittleness (Irfan et al., 2015; Wasilewska and Winnicka, 2019). It can be determined using texture analyzer — usually, the film is placed in holder while a probe moves at a constant speed until the film is broken (Wasilewska and Winnicka, 2019).

4.2.5. Moisture content

When water, or other solvents, remains in an ODF in high amounts it can lead to stickiness and growth of micro-organism (Visser et al., 2015). Likewise, when to little moisture remains in an ODF is can become too brittle (Wasilewska and Winnicka, 2019). To assess moisture content, the Karl Fisher titration method can be used, or pre-weighed ODFs can be heated above 100°C and re-weighed to quantify mass loss (Visser et al., 2015; Wasilewska and Winnicka, 2019).

4.2.6. Folding endurance

It is representative of an ODF’s flexibility and is determined by folding a particular film several times until it breaks (Irfan et al., 2015; Wasilewska and Winnicka, 2019). While there is not set number of folds a film must withstand, a film that can be folded three hundred times is thought to have excellent flexibility (Wasilewska and Winnicka, 2019).

4.2.7. Surface pH

The surface pH of an ODF should be determined to ensure the formulation will not cause mucosal irritation from being too acidic or basic (Irfan et al., 2015). The surface pH can be determined by using a pH meter electrode on a wet film (Irfan et al., 2015).

4.2.8. Dryness/tack test

This test is used to determine the ODFs ability to stick to a piece of paper, which is representative of the films tack (Irfan et al., 2015; Wasilewska and Winnicka, 2019). This test can be used to determine how an ODF should be packaged and handled (Wasilewska and Winnicka, 2019).

4.2.9. Swelling property

Using a wire mesh, a weighed ODF is submerged in simulated saliva and the increase in ODF weight is measured (Dey and Ghosh, 2016; Irfan et al., 2015). This procedure is repeated at set time intervals until the weight increase is constant and then the difference in weight before and after contact with simulated saliva is calculated (Irfan et al., 2015).

4.2.10. Transparency

In addition to visual appearance consistency, knowing the transparency of an ODF can be useful when assessing the stability of the formulation (e.g., loss of transparency over time) (Wasilewska and Winnicka, 2019). One way transparency can be determined is by cutting the films into rectangles, placing them inside an ultraviolet spectrophotometer cell, measuring the transmittance of the film at a specific wavelength (e.g., 600 nm) and determining transparency using a mathematical equation (Irfan et al., 2015). Besides, the transparency of an ODF can be evaluated using qualitative methods such as visual inspection (Hamza, 2017).
4.2.11. Disintegration time

Like ODTs, a short disintegration time, between 5 – 30 s (generally below 60 s) is a desirable characteristic of ODFs. Two ways disintegration time of an ODF can be measured are the drop method and the petri dish method. In the drop method, a drop of distilled water is placed on the sample ODF, and the time required to break the film apart is measured. With the petri dish method, on the other hand, a petri dish containing the ODF and about 2 mL of distilled water, is shaken continually and the time required for the film to fully disintegrate is recorded (Preis and Breitkreuz, 2012; Pezik et al., 2021; Desai et al., 2022).

5. Pharmacokinetics in paediatrics

It is well known that pharmacokinetic differences exist between the paediatric and adult populations (Batchelor and Marriott, 2015). Moreover, pharmacokinetic differences exist between children of different age groups due to the several physiological changes that take place as a child grows (Batchelor and Marriott, 2015). Accordingly, it is important to look at the pharmacokinetic parameters of orodispersible drug carriers specifically in minors. Orodispersible drug carriers are proposed to offer a rapid drug onset due to the rapid disintegration in the oral cavity (Kapse et al., 2015). In addition to absorption via the gastrointestinal tract, they have the potential for absorption in the oral cavity which can result in a higher bioavailability of the drug, by bypassing first-pass metabolism, and again, an increased onset of action (Kapse et al., 2015). While there is currently limited evidence detailing the pharmacokinetics of orally disintegrating formulations in paediatrics, two studies sought to investigate this topic.

Wang and colleagues investigated the use of raccadotril, an antidiarrheal drug, as an ODF in the paediatric population (Wang et al., 2021). To prepare the ODFs, the researchers used the solvent casting method. To investigate the pharmacokinetic profile, four healthy beagle dogs were used. As a comparator to the ODFs, commercially available raccadotril dry granules were made into a suspension. The pharmacokinetic parameters investigated included area under the curve, maximum plasma concentration, peak time, elimination half-life, and relative bioavailability. The researchers concluded there was no statistically significant difference between the optimized ODF and the commercially available raccadotril granules and deemed them bio-equivalent. Although upon examination of the results, the trend in results did seem to favour the granules compared to the ODF: maximum plasma concentration and area under the curve were higher for the granules in suspension and the time to peak was longer for the ODF despite being non-significant.

Faisal et al. conducted a study that compared the pharmacokinetic differences of enalapril as child friendly ODMTs to standard enalapril tablets (Faisal et al., 2019). To do so, three treatment arms were prepared and administered to twenty-four adults: enalapril tablets with 240 mL of water, ODMTs with 240 mL of water, and ODMTs dispersed in the mouth with 20 mL of water. Pharmacokinetic variables of interest included the rate constant of absorption and elimination, the volume of distribution, and the relative bioavailability. Results showed that enalapril administered as an ODMT with 240 mL of water had the faster rate of absorption, appearing 4 min earlier in the serum. No other significant differences were observed between the three treatment arms.

As evident by the two studies discussed above, the use of orodispersible drug carriers in the paediatric population offers an at least as good, if not better, pharmacokinetic profile as conventional drugs forms found on the market. Understandably the current evidence is not sufficient to make any definitive claims about the pharmacokinetics of orodispersible dosage carriers in the paediatric population given the several limitations of the individual studies. One being the small sample population in both studies and the probable poor external validity. Perhaps the most notable limitation is the lack of paediatric participants used to conduct the research. More research detailing the pharmacokinetics of orodispersible drug carriers in this population would be of great benefit.

6. Advantages and limitations of their use in minors

There are several reasons supporting why orodispersible drug carriers are preferred over more traditional paediatric dosage forms like tablets, capsules, and oral liquids. Orodispersible drug carriers allow for an easy administration process, for both the child and caregiver, by diminishing the need for water, avoiding the need for measuring devices, and minimizing choking risk (Dey and Maiti, 2010; Lopez et al., 2015). Unfortunately, orodispersible drug carriers can cost significantly more than traditional dosage forms due to the special equipment and packaging often required (Lopez et al., 2015). The high cost typically associated with orodispersible drug carriers may limit accessibility in the paediatric population. Additionally, they are generally restricted to children 6 months of age or older and taste masking is particularly challenging in high dose formulations (Cornilla et al., 2022). Thus, the benefits of orodispersible drug carriers must be weighed against any potential restrictions. Summarized in Table 3, are the common advantages and limitations of orodispersible drug carriers for use in the paediatric patients.

7. Future direction and recommendations

Orodispersible drug carriers have the potential to increase medication compliance and treatment success for the majority of patients (Dey and Maiti, 2010). It has been stated frequently throughout the literature that the favourable properties of orally disintegrating preparations including rapid disintegration time, lack of water needed, compact size, and possibility for taste-masking offer an ideal oral dosage form for the paediatric population (Wiedey et al., 2021). Yet, there is still a significant shortage of commercialized orally disintegrating medicinal products solely dedicated for use in minors and this remains one of the

<table>
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<tr>
<th>Table 3</th>
<th>Benefits and drawbacks of using orally disintegrating formulation in paediatric patients</th>
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<tbody>
<tr>
<td>Advantages</td>
<td>References</td>
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<tr>
<td>No water is required for administration</td>
<td>(Dey and Maiti, 2010)</td>
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<tr>
<td>Improved stability as compared to oral liquid dosage forms</td>
<td>(Dey and Maiti, 2010)</td>
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<tr>
<td>Accurate dosing compared to oral liquids</td>
<td>(Dey and Maiti, 2010)</td>
</tr>
<tr>
<td>Decreased risk for choking compared to traditional tablets and capsules</td>
<td>(Dey and Maiti, 2010)</td>
</tr>
<tr>
<td>Small packaging compared to oral liquids</td>
<td>(Dey and Maiti, 2010)</td>
</tr>
<tr>
<td>Does not require spoons, cups, or syringes for administration</td>
<td>(Preis, 2015)</td>
</tr>
<tr>
<td>Potential for absorption via the oral mucosa and improved bioavailability of the drug</td>
<td>(Kapse et al., 2015)</td>
</tr>
<tr>
<td>Rapid disintegration of the drug, leading to rapid onset of action</td>
<td>(Kapse et al., 2015)</td>
</tr>
<tr>
<td>Improved patient compliance and subsequently improved therapeutic outcomes</td>
<td>(Dey and Maiti, 2010)</td>
</tr>
<tr>
<td>Decreased caregiver burden owing to the easy-to-use dosage form</td>
<td>(San et al., 2008)</td>
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<tr>
<th>Limitations</th>
<th>References</th>
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<tr>
<td>Limited drug loading capacity</td>
<td>(Kapse et al., 2015)</td>
</tr>
<tr>
<td>Special storage often required due to moisture sensitivity</td>
<td>(Wang et al., 2021)</td>
</tr>
<tr>
<td>Unpleasant taste and/or mouth feel requiring flavouring agents</td>
<td>(Wang et al., 2021)</td>
</tr>
<tr>
<td>Safety of all excipients in the paediatric population not-well understood</td>
<td>(Lopez et al., 2015)</td>
</tr>
<tr>
<td>Not suitable for drugs that irritate the oral mucosa</td>
<td>(San et al., 2008)</td>
</tr>
<tr>
<td>High cost of production due to specialized manufacturing approaches and technologies</td>
<td>(Ozyilmaz et al., 2018)</td>
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greatest challenges with the full implementation and acceptability of this dosage form globally. Antibiotics, respiratory, and nervous system therapeutic agents are the most used medications in children and adolescents (Servais et al., 2021). Despite this knowledge, little or no approved marketed orodispersible dosage forms exist for these medical conditions. For instance, an antibiotic orodispersible delivery system could be especially useful given antibiotic suspensions are one of the only orally available options for children who cannot swallow or chew tablets. Various researches into the development of orally dispersible antibiotic formulations have begun, including formulations of levofloxacin and ciprofloxacin (Asha et al., 2018; Kagsavade and Swapnil, 2016). However, in both cases the paediatric population was not the target. Thus, future research and development involving the optimal design of these frequently used classes of drugs into smart orally disintegrating matrices for paediatric pharmacotherapy is crucial.

Challenges associated with the successful fabrication and optimal performance of orally disintegrating drug delivery systems require more attention and improvements. As previously mentioned, these carriers have limited drug loading capacity, which is problematic for drugs that require high doses to elicit the desired pharmacological effects. Furthermore, taste-masking strategies are also required for these dosage forms to ensure wide acceptance among paediatric patients and their caregivers. Lastly, the mechanically friable and hygroscopic tendencies of most orally disintegrating dosage forms often result in the need for specialized foil type packets and storage requirements which are generally more expensive than traditional packaging approaches. Thus, further in-depth investigations are needed to overcome these formulation challenges and optimize this class of delivery systems, particularly for widespread use in children and adolescents.

8. Conclusion

Orally dispersing drug carriers overcome several of the challenges associated with conventional paediatric oral dosage forms. Numerous orodispersible formulations have been investigated for paediatric use and this include tablets, mini-tablets, films, webs, fibers, granules, and capsules. Application of these delivery systems has provided the opportunity for the use of potentially more beneficial alternative treatment approaches for the management of various paediatric ailments. Given the increasing use of this dosage form, the manufacturing process and quality control aspects is still continually changing and expanding. Several excipients can be utilized in the development of orodispersible drug carriers; however, the safety of these excipients in minors must be thoroughly understood before they can be applied. The pharmacokinetic of orally dispersing delivery systems in paediatric patients is still being understood, however it is reasonable to conclude these dosage form provide sufficient bioavailability while offering rapid disintegration. Intensifying research and innovation activities on orodispersible carriers designed as tablets (including mini-tablets), films and wafers/lyophilisates, which we consider the more flexible, tunable, easily scalable, and child-friendly forms of orally dispersing delivery systems, is likely to result in improved adherence and therapeutic outcomes in minors, particularly those age two years and old and above.

CRediT authorship contribution statement

Emma A. Kean: Writing – original draft, Writing – review & editing, Investigation, Methodology, Visualization. Oluwatoyin A. Adeleke: Conceptualization, Methodology, Investigation, Visualization, Writing – review & editing, Funding acquisition, Project administration, Supervision.

Declaration of Competing Interest

None.

Data Availability

No data was used for the research described in the article.

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References
