INNOVATIVE DELIVERY SYSTEMS FOR PAEDIATRIC MEDICINES

TECHNOLOGY LANDSCAPE

Unitaid
Innovation in Global Health

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Innovative delivery systems for paediatric medicines:
technology landscape

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INNOVATIVE DELIVERY SYSTEMS FOR PAEDIATRIC MEDICINES: TECHNOLOGY LANDSCAPE

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FOREWORD

There has been tremendous progress towards reducing morbidity and mortality from the major infectious disease killers including HIV, tuberculosis, and malaria. This is due in part to the introduction of innovative treatments and diagnostic tools which have contributed to greater efficiencies of care, moving us closer to our targets for eliminating these diseases as a public health problem. However, significant gaps in the global response remain and progress continues to be slower in key and vulnerable populations, including infants and children. Still over 5 million children are dying before reaching their fifth birthday, mostly in low and middle-income countries, and mostly from conditions that are readily preventable or treatable.

Medicines recommended for the prevention or treatment of diseases in babies and children are frequently legacy medicines which may not be the most effective, and/ or are delivered as non-palatable complicated dosage forms eventually leading to poor adherence and inadequate dosing of the prescribed treatment. Many challenges affect the investigation, development and access of appropriate medicines for children including weak market incentives with limited prospectus of market revenue; logistical, operationaland technical barriers; and complex evaluation and regulatory pathways.

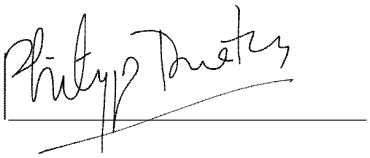
Over the last years, several global stakeholders have worked towards accelerating access to optimal paediatric formulations, whose availability historically have lagged up to 10 years behind that of the adult treatments. The World Health Organization (WHO), at the heart of such collaborative efforts, organized the first Paediatric Antiretroviral Drug Optimization (PADO) meeting in 2013 in Dakar to examine gaps in HIV-paediatric formulations to ensure best recommendations on the use of antiretroviral drugs could be implemented for treating and preventing HIV infection in infants and children, as well as to support the investigations and development of more simplified, less toxic drug regimens. Since then, paediatric drug optimization has expanded to other disease areas promoting prioritization and adaptation of key drugs and regimens for tuberculosis and hepatitis. The establishment of the Global Accelerator for Paediatric Formulations (GAP-f), launched in 2018 and now formally recognised as a WHO-led network, provides an opportunity to reinforce and innovate the mechanism needed to ensure that priority optimal paediatric formulations are investigated, developed and made available to children in a timely manner. Within malaria, revisions were made to the co-payment structure of Affordable Medicines Facility – Malaria (AMFm) to favour paediatric packs for therapies in March 2011. Since the revisions, measures have been put in place for managing orders to give preference to child-packs – which had an immediate impact on uptake of these medicines for children in affected regions. In addition, key research and development efforts have played a major role in bringing in more competition with the entry of multiple generic products pushing down prices for malaria medicines, both for adults and children.

In recent years, various improved child-friendly formulations have come to market, as a result of a multi-stakeholder approach, for critical medicines for HIV (e.g., ritonavir-boosted lopinavir oral pellets), malaria (e.g.., dispersible sulfadoxine--pyrimethamine + amodiaquine) and tuberculosis (e.g., dispersible fixed dosed combinations for first-line treatment). These more effective formulations and regimens are lessening the burden for

health providers and caregivers administering the medicines and offering more adapted and acceptable treatment options for children taking the medicines. Furthermore, they are demonstrating greater tolerability in young children and infants and leading to better health outcomes. Unitaid has been at the forefront of these efforts with over US$1 billion direct investments since its inception put towards improving and accelerating therapeutic innovations for children affected by HIV, tuberculosis, and malaria in low- and middle-income countries.

Much more remains to be done. Innovative delivery tools hold promise in facilitating cost-effective fit-for-purpose products that meet the unique needs of children in low-resource settings around the world. These tools could further simplify administration, improve adherence and ultimately lead to better health outcomes in children. This potential needs to be fully tapped starting with thorough landscaping to identify opportunities to accelerate research and development for the maximum impact. We cannot let infants and children be left behind and suffer and die from treatable conditions; we cannot accept the status quo and need to ensure that the most vulnerable, the small children, are at the forefront of our efforts in scientific and technical innovation.

Signatures



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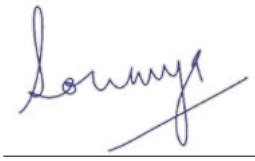

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ABBREVIATIONS AND ACRONYMS

3DP	3-dimensional printing
AMFm	Affordable Medicines Facility – Malaria
ARV	Anti-retroviral (drug)
ASD	Amorphous solid dispersion
CHAI	Clinton Health Access Initiative
DT	Dispersible tablet
EC	European Commission
FDA	Food and Drug Administration
GI	Gastro-intestinal
GRAS	Generally Recognized as Safe
IER	Ion exchange resin
IM	Intra-muscular
IV	Intra-venous
LMIC	Low and Middle-Income Countries
mcg	microgram
mg	milligram
MHRA	Medicines and Healthcare Regulatory Authority
mL	millilitre
MP	Multi-particulate
nm	nanometre
ODMT	Oro-dispersible mini tablet
ODT	Oro-dispersible tablet
SC	Sub-cutaneous
SEDDS	Self-emulsifying drug delivery system
SLN	Solid lipid nanoparticle
SMEDDS	Self-micro-emulsifying drug delivery system
SNEDDS	Self-nano-emulsifying drug delivery system
TPP	Target product profile
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization

EXECUTIVE SUMMARY

Although morbidity and mortality of children has declined significantly from the major infectious diseases such as TB, malaria, HIV and HIV-associated infections, **this vulnerable population still suffers disproportionately from low coverage of preventive and treatment interventions, poor outcomes and high-mortality compared to adults. A major driver of this is the real lack of fit for purpose products for children in LMICs and this is true not only for the therapeutics for the diseases mentioned, but also for antibiotics and other therapeutics listed on the WHO Essential Medicines List and medicines for neglected diseases in general.**

Age-appropriate formulations and improved case finding have allowed greater gains in reducing morbidity and mortality in children, although critical gaps still remain. For instance, delivery of these interventions continues to present challenges, particularly in low- and middle-income countries, which are exacerbated at time of systemic disruptions (i.e., outbreak and conflict) affecting uptake and compliance. In this context, **one area of great interest is novel delivery and formulation methods for medications geared to the unique needs of children which can overcome or mitigate some of the larger systemic or individual challenges still reported.**

Paediatric patients are a highly diverse patient population ranging from pre-term and term neonates to adolescents, which makes the development of paediatric medicines very challenging. Changes in drug metabolism and clearance require dose adjustment based on age and weight which affect our ability to design dosage forms with maximum flexibility. It is also key to consider the acceptability of a paediatric medicine to facilitate patient compliance; aspects such as palatability, dose volume and frequency, complexity of administration (for example reconstitution or mixing with food or beverage) and the potential for administration to cause pain or discomfort are key.

The development of paediatric medicines in adequate formulations for LMICs has additional challenges including compatibility with high temperature and high humidity climates, transportation systems that are rudimentary and fragmented, poorly developed supply chains, high cost of paediatric formulations and difficulties for caregivers to store and administer them appropriately.

Additionally, conducting clinical studies in paediatrics is more challenging and may be more costly than adult studies. This often requires the set-up of multi-country studies with multiple sites recruiting a small number of participants in each. Research capacity to meet appropriate standards to undertake these studies continues to be limited in some regions of the world and efforts need to put in place for training and monitoring.

Overall, the cost of the research and development of **licensed paediatric products may be greater than for products intended for adults and lack market incentives.** With unclear and limited market prospectus, such as for LMICs markets, these development programs do not take place in the absence of intervention.

Introduction and uptake of new paediatric products remain the last critical steps of and effective path to children in need. These aspects are often overlooked with the expectation that products will make their way to children in need, but there are multiple examples of significant delays in paediatric products uptake.

Provided in this landscape analysis is an overview of new and emerging dosage forms and formulation technologies that may be beneficial if applied for use in paediatric patients. It covers various routes of administration including oral, rectal, parenteral, transdermal and others. There is also attention given to long-acting formulations that hold clear promise for use in children. **Emphasis is placed upon those dosage forms and technologies which could be suitable for use for children in LMICs**.

There are key considerations when analysing potential application of these technologies to existing and emerging therapeutic needs for children. **Some technologies are ready and available to use in an intervention today, while others will require further investigations**. As a result, strategic interventions and investments in this area can be classified by opportunities in the short-term and in the long-term.

There are near-term opportunities for the development of age-appropriate solid oral dosage forms including dispersible tablet formulations and oro-dispersible tablets. Also, suppositories and long-acting depot injectables offer potential alternatives and are gaining interest. Well established technologies for controlling and delaying release and for enhancing the bioavailability of poorly soluble drugs are all considered to provide near-term opportunities. On the longer term, further evaluation of the safety and acceptability of some of the dosage forms and technologies in paediatric patients are required, as well as, the feasibility for cost-effective commercialisation. (i.e., oro-dispersible and buccal films, long acting implants, and needle-free injections).

Stakeholders involved with development of target product profiles and prioritization of formulations for children should be aware of the available delivery systems and formulation methods to be able to focus efforts on the best fit technology for a specific condition or medicine affecting children in LMICs that could have the most positive impact.

There is urgency to review therapeutic gaps for children that could be addressed with better formulations of life-saving medicines and match them with available technologies to ensure full realization of the potential of existing medicines when adequately formulated.

1. LANDSCAPE OBJECTIVE

Unitaid's mission and approach is to utilize market interventions to improve public health and catalyse access to better health products in low and middle-income countries (LMICs). Across its portfolio in HIV and its comorbidities, TB, and malaria, Unitaid has invested significantly in better treatment and diagnostics for children. Through its investments and with its partners including WHO, Unitaid supports key activities to speed access to priority products for children notably for children affected by with HIV and its coinfections, TB, and malaria.

Age-appropriate formulations and improved case finding have allowed greater gains in reducing morbidity and mortality in children, although critical gaps remain. Given the state of the art of existing and pipeline technologies to deliver medicines, there is the possibility of determining opportunities for further addressing the treatment needs of this vulnerable population. One area of promise is novel delivery and formulation methods for medications geared to the unique needs of children.

This landscape analysis provides an overview of various paediatric medicine delivery solutions with a focus on disease-agnostic technologies that could be adapted to priority diseases in LMICs and could guide the planning for strategic investments in this area.

2. METHODOLOGY

This landscape document has been prepared using information in the public domain, including peer-reviewed publications identified through literature searches, scientific news articles (January 2019 – March 2020), individual websites of regulatory and policy agencies (EMA, US FDA, MHRA and WHO-PQ), and company websites.

Additional information regarding existing and emerging technologies that may be applicable to paediatric patients has been sourced via interviews with key opinion leaders and researchers (January – February 2020). Data and analysis are current as of 10 April 2020, unless otherwise indicated.

3. PUBLIC HEALTH CHALLENGES IN PAEDIATRIC TREATMENT AND PREVENTION

Although morbidity and mortality of children has declined significantly from the major infectious diseases such as TB, malaria, HIV[1] and HIV-associated infections, this vulnerable population still suffers disproportionately from low coverage of preventive and treatment interventions, poor outcomes and high-mortality compared to adults.

There is real lack of fit for purpose products for children in LMICs and this is particularly true for not only the therapeutics for the diseases mentioned above, but also for antibiotics and other therapeutics listed on the WHO Essential Medicines List for children (EMLc). In addition, there are increasingly new medicines emerging from the pipeline that are transforming care for many conditions, including neglected diseases such as such as leishmaniasis, Chagas disease and sleeping sickness. The importance of enabling these life-saving products for use in children in a timely fashion is essential, with consideration of the most critical needs and pressing opportunities. It will be paramount to ensure that these new molecules are evaluated in a timely fashion in clinical trials for an indication in children, as well as, formulated in a child-friendly and effective manner.

4. MARKET BARRIERS TO PAEDIATRIC MEDICINE DEVELOPMENT

4.1 Technical challenges

Paediatric patients are a highly diverse patient population ranging from pre-term and term neonates to adolescents, which makes the development of paediatric medicines very challenging. Childhood is a period of rapid growth and development which impacts the way drugs are metabolised and cleared, and hence the required dose of a drug can change with age. In addition, exposure to excipients in children may differ compared to that in adults. Although excipients are generally considered to be inert components of formulations, they may have a different effect on the developing organ systems of a child. Therefore, the safety and toxicity of excipients used in medicines intended for paediatric patients need to be assessed and their use and levels justified. Excipients of concern include preservatives, colouring agents, flavourings, sweetening agents, surfactants and co-solvents.

The ability of children to take different dosage forms and suitable dose volume also changes according to age. For example, it is well recognised that neonates, and infants but also young children may have difficulty in swallowing large solid oral dosage forms, and children below the age of approximately 4 years have difficulty in using dry powder inhalers. In addition, appropriate volumes of liquids (oral, parenteral, rectal, nasal) for paediatrics are smaller than those for adults, and therefore may require the use of different-sized administration devices or different concentrations to ensure acceptable accuracy of dose.

It is key to consider the acceptability of a paediatric medicine to facilitate patient adherence; aspects such as palatability, dose volume and frequency, complexity of administration (for example reconstitution or mixing with food or beverage) and the potential for administration to cause pain or discomfort are key. Furthermore, socio-cultural factors and familiarity with a dosage form type should be considered. All these aspects can impact adherence and ultimately affect outcomes.

This may result in the need for more than one paediatric dosage form and/or strength, which can lead to added complexity and cost. Indeed, an "ideal dosage form" generally does not exist and therefore a compromise may need to be reached.[2,3,4,5,6,7,8,9,10]

The development of paediatric medicines for LMICs has additional challenges. Many LMICs have high temperature and high humidity climates. Therefore, since there is limited provision of temperature-controlled supply chain and storage in these areas, drug products should be stable at elevated temperatures and humidity. Solids tend to be more stable than liquids and semi-solids, and therefore may be more suitable for such climates. Furthermore, transportation systems can be rudimentary and fragmented, especially in rural areas, resulting in the need for lightweight and compact yet robust primary packaging. Poorly developed supply chains can also lead to difficulties in effective distribution of medicines. The price of pharmaceutical products is a key selection criterion in LMICs with low availability and/or poor affordability (cost equivalent to a day or more day's wages) being key barriers to patients' access to potentially better products.[11,12,13]

4.2 Paediatric clinical studies

Conducting clinical studies in paediatrics is more challenging and may be more costly than adult studies for several reasons. For example, optimizing study design to generate the right evidence might not always be straightforward from the start and while small pharmacokinetic studies are often sufficient to prove appropriate exposure of an approved drug when testing a new formulation, there are instances where larger efficacy or safety studies might be of value such as in special populations such as neonates or young infants. Identifying these specific cases and designing studies optimally so that the largest amount of evidence is generated in the shortest possible time can be a challenge. Moreover, the recruitment and accrual of an appropriate number of children across age groups can be time-consuming and difficult due to a relatively small patient population when the target diseases are less prevalent. This often requires the set-up of multi-country studies with multiple sites recruiting a small number of participants in each. Research capacity to meet appropriate standards to undertake these studies continue to be limited in some regions of the world and efforts need to put in place for training and monitoring.

Parents/caregivers may be reluctant to allow their child to participate in a clinical study due to concerns regarding safety, for example possible side effects, and the need for blood sampling, which may deter them from providing informed consent. Depending on national regulations, older children may be required to give their assent for participating and may have similar concerns. Logistical deterrents may include lack of transportation to study site and conflicts with work and school schedules. There are also ethical challenges associated with conducting studies in children. Ethical review boards are at times reluctant to approve clinical studies without substantial evidence in adult populations. For example, it is unethical to allow a child to participate in a clinical study if there is no perceived direct benefit for him or her, and potential risks need to be carefully managed. The volume of blood taken through sampling must be limited and paediatric studies should be designed such that the number of sampling points per patient is minimised whilst ensuring sufficient collation of data. In resource poor areas, additional challenges for conducting

paediatric studies include lack of patient accessibility to healthcare facilities and limited ethical committee and regulatory experience in reviewing and approving clinical studies in children.[14,15,16,17]

4.3 Cost, regulations and incentives

Overall, the cost of the development of paediatric products may be greater than for products intended for adults, due to the challenges and potential need to develop more than one formulation to allow easy administration to children across all age groups. In addition, the cost of manufacturing specialised formulations, especially when weighed against the return on investment and particularly for small markets or niche products, can be high compared to well-established, non-complex formulations manufactured on a large scale.

This lack of market incentives has required the establishment of specific regulatory frameworks that both in the US and EU have ensured that infants and children are included in drug development programmes, unless otherwise justified. However, these regulations, have so far only influenced patent-protected drugs to be marketed in high-income countries (for example, USA and Europe) and very minimally drugs with a market outside of these territories.[18,19,20] In addition, the timelines for completion of paediatric investigation plans to generate sufficient data or due to delays can often take several years to obtain a paediatric indication after a new drug receives marketing authorization for adults.

In contrast, the development of paediatric medicines of off-patent drugs is currently voluntary, with potentially limited financial incentives or rewards for pharmaceutical companies; many off-patent paediatric medicines under development have been made available through research consortia projects financed with public and philanthropy funds. As a result, there is still a lack of age-appropriate products of off-patent drugs, including for drugs being used to treat priority diseases in LMICs.[21,22] Dedicated incentives need to be explored on a product by product basis.

4.4 Product introduction and roll out

Introduction and uptake of new paediatric products remain the last critical steps of and effective path to children in need. National registration, inclusion in national treatment guidelines, and national formularies are all essential steps to introduce a new paediatric product. Programmes are then in charge to generate demand where children primarily receive care, conducting adequate training, supported supervision and effective management of the supply at national and subnational level. This is particularly true for new formulations with complex preparation and administration requirements, which might be challenging in resource-limited settings.

These aspects are often overlooked with the expectation that newer, better products will make their way to children in need, but there are multiple examples of significant delays in the uptake of paediatric products. Delayed uptake and limited demand represent further disincentives for any additional investment to scale up manufacturing capacity and ensuring supply continuity for paediatric formulations.

Over the last few years, rapid introduction and effective roll out of any new paediatric product have therefore required catalytic investments to ensure adequate planning and proactive coordination among the various stakeholders involved. In the foreseeable future these interventions will continue to be important to ensure innovative products make it to the end of children in need.

5. TECHNOLOGY LANDSCAPE

An overview of new and emerging dosage forms and formulation technologies that may be applicable for paediatric patients is provided in this section, including examples of marketed products in each case, even if to date only developed for adults. Emphasis is placed upon those technologies which could be suitable, and beneficial, for use for children in LMICs. The technology landscape is disease agnostic and does not include information on new therapeutic compounds but only in the technologies to be applied as appropriate to improve their formulation and convenience for children.

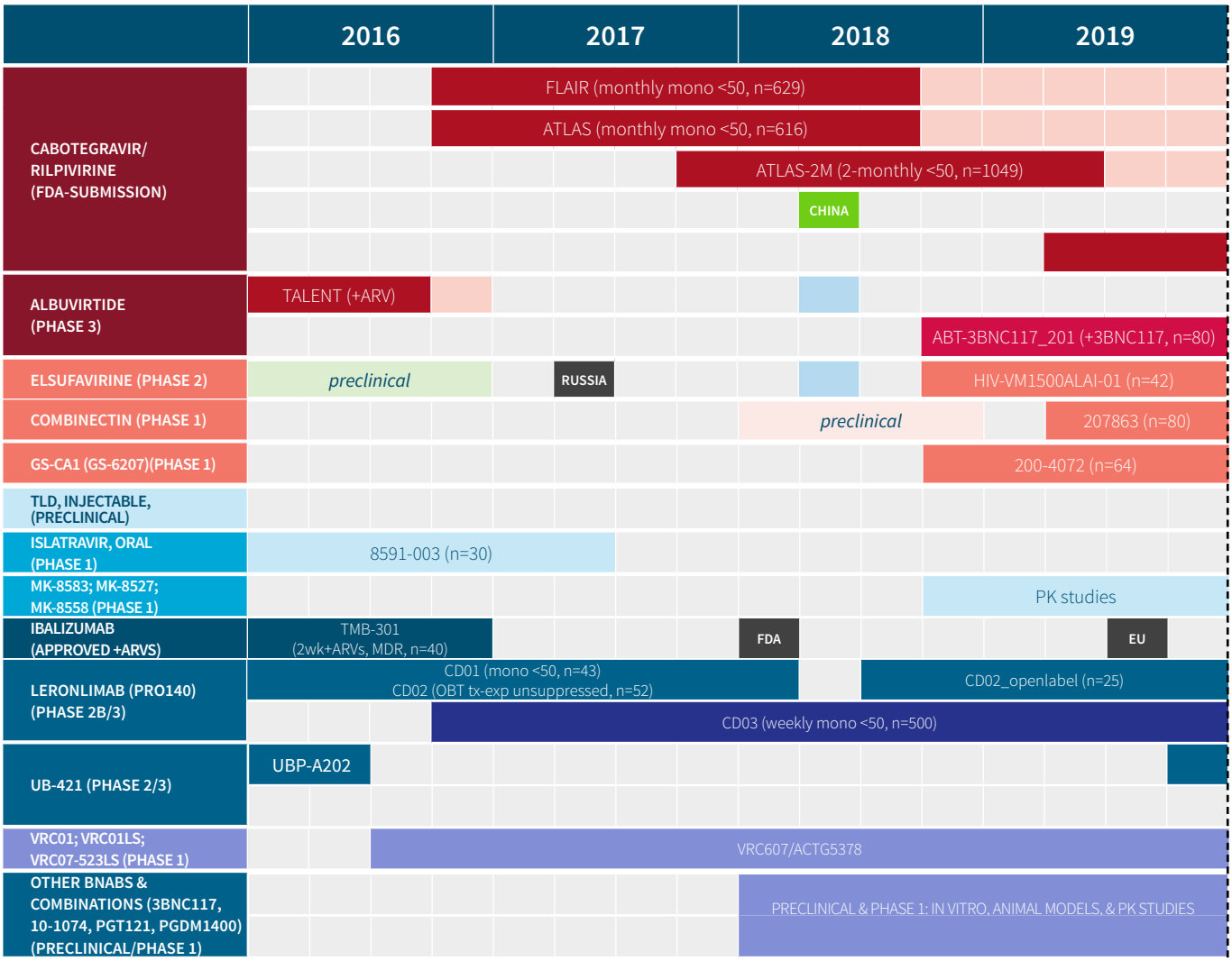
The landscape is divided by route of administration:

- Oral route (chapters 5.1)
- Rectal route (chapter 5.2)
- Parenteral route (chapter 5.3)
- Transdermal route (chapter 5.4)
- New technologies applicable to different routes (chapter 5.5)

In addition, in each case special attention has been given to **long-acting formulations** to further assess the potential of this approach for children in each of the relevant routes of administration (oral, parenteral and transdermal). Controlled (sustained) drug release has several advantages including the optimisation of pharmacokinetics, reduction in dosing frequency, improvement in patient compliance and simplification of mass drug administration campaigns. Facilitating adherence and retention in care is of particular importance for chronic conditions, and infections where a lack of adherence could lead to the development of drug resistance and treatment failure.

This has led to an interest in the research and development for long acting drugs and products for HIV treatment and prevention (e.g. antiretrovirals such as islatravir, or HIV-1 capsid inhibitors, or broadly neutralizing antibodies, but also by formulating short-acting antiretrovirals with technology platforms and devices that can extend their life up to one year, such as cabotegravir for pre-exposure prophylaxis) as reflected in **Figure 1** and **2** below. [23]

FIGURE 1 Landscape of long-acting HIV treatment pipeline (Unitaid/WHO, December 2019)



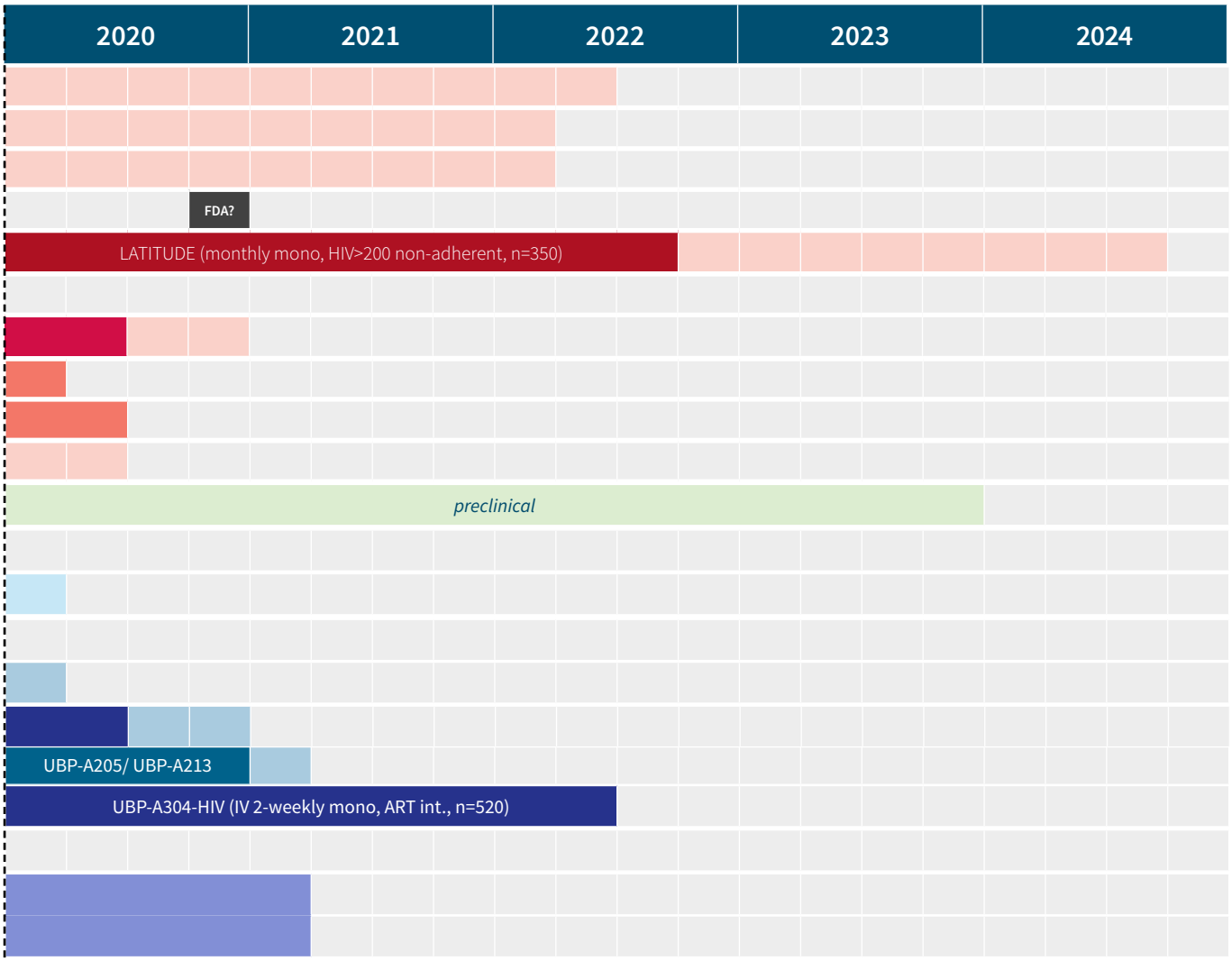
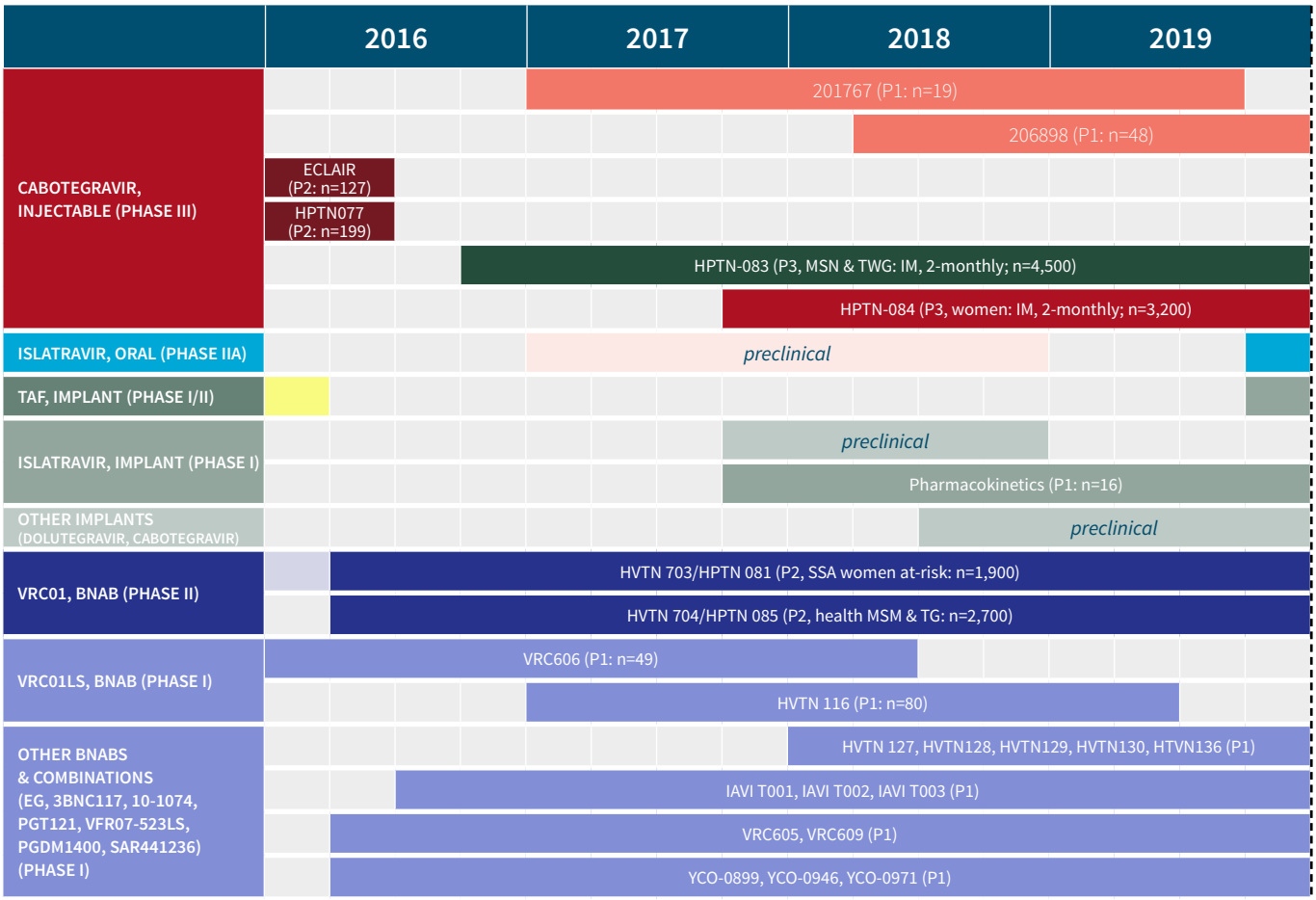
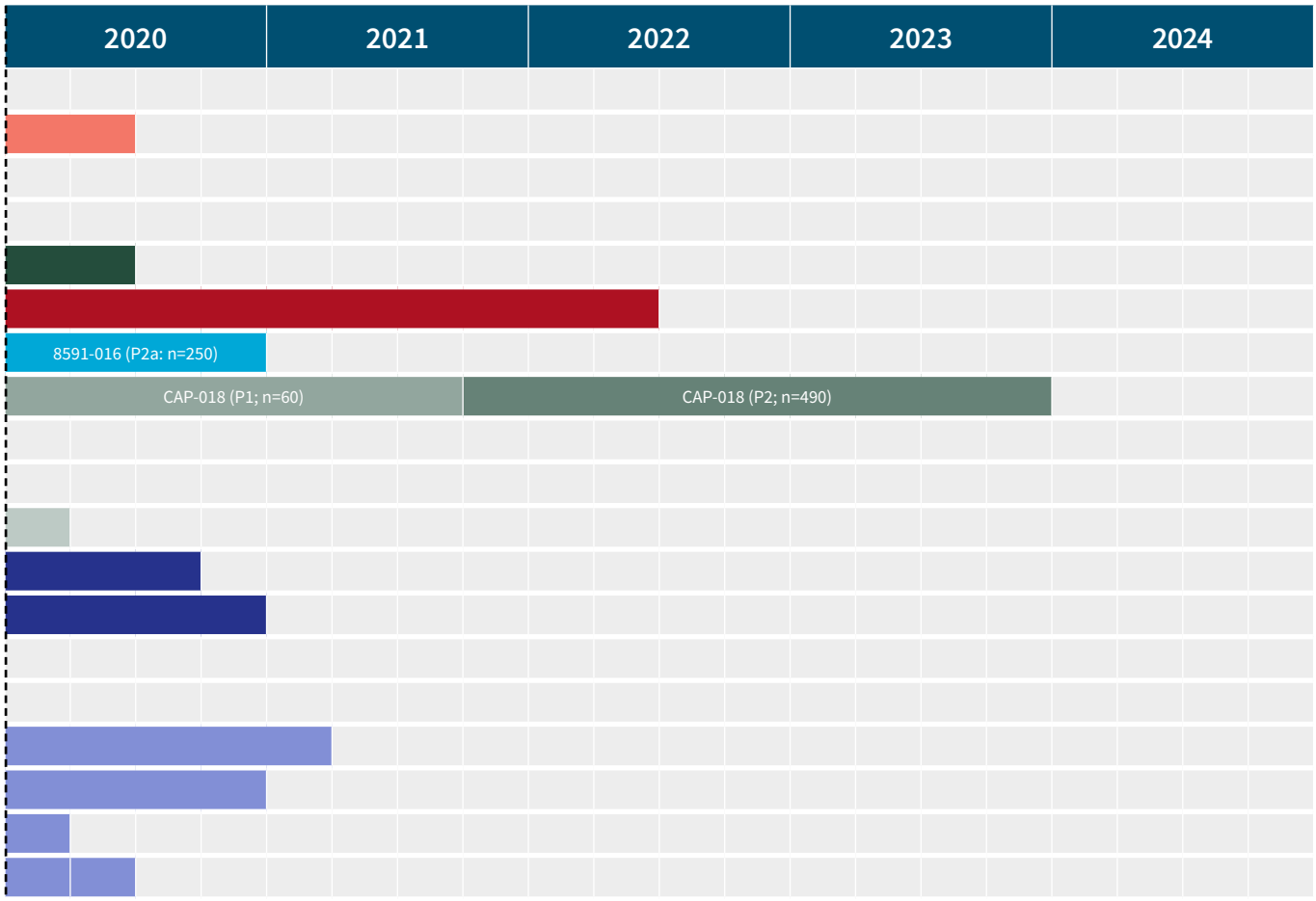

2020
2021
2022
2023
2024
FDA?
LATITUDE (monthly mono, HIV>200 non-adherent, n=350)
preclinical
UBP-A205/ UBP-A213
UBP-A304-HIV (IV 2-weekly mono, ART int., n=520)

FIGURE 2 Landscape of long-acting HIV prevention pipeline (Unitaid/WHO, December 2019, adapted May 2020)





Likewise, a number of products are now also under investigation in the field of long-acting for other indications such as malaria, TB or hepatitis C.[24,25] This is in addition to the continued improvement of long-acting contraceptives and the search for combined use long-acting products, for example for contraception and HIV prevention.[26,27] A review of long acting technologies (for oral and non-oral routes of administration) for the prevention and treatment of major infectious diseases has been conducted by Unitaid [28], some of which may potentially be applicable to paediatrics.

5.1 Oral route dosage forms and technologies

The oral route is a commonly used route for medicine administration to paediatrics, although as discussed above, the acceptability of different dosage forms varies according to the age and developmental stage of the child. Oral liquids (solutions, suspensions, emulsions) are acceptable from birth, being easy to swallow and allowing flexibility of dosing. However, due to their limited stability in non-temperate climates and potentially bulky primary packaging, they have not been included in this document. Indeed, the WHO has stated that "the dosage forms of medicines that are likely to prove most "suitable" particularly for developing countries are flexible solid dosage forms, such as tablets that are oro-dispersible and or that can be used for preparation of oral liquids (for example suspension or solution)."[29] Chewable dosage forms may be preferred by children aged from approximately 6 years and are frequently used to administer vitamins to school age children. However, there is a risk of choking or aspiration in young children and hence they are not discussed in this document. Conventional tablets and capsules have also been excluded since they are generally only acceptable for older children and adolescents.

5.1.1 Dispersible tablets

Dispersible tablets (DTs), also known as tablets for oral suspension, are uncoated tablets or film-coated tablets that disintegrate into a homogenous dispersion within 3 minutes in water (or another beverage, e.g. breast milk) before administration. DTs are often packaged in blister packs.

5.1.1.1 Advantages and Disadvantages

DTs are generally more stable than liquids, are less bulky and do not require preservatives. However, they can be susceptible to moisture and therefore may require moisture protective packaging such as aluminium, which can be more expensive than plastic blister packaging. A moisture-protective blister system has been developed by Amcor (Dessiflex Blister System) that incorporates desiccant particles into the aluminium sealant layer to help absorb moisture.[30] This may improve the stability and shelf-life of moisture-sensitive products and drugs, but it should be noted that excessive drying of some formations can lead to friability. DTs have limited dose flexibility although they enable straightforward accurate dosing in patients with swallowing difficulties and are simple and easy to prepare and administer. It is important that a minimal volume of liquid is used for dispersion and that the whole volume is administered to ensure the full dose is taken. The lack of clean water in low-resource settings can present another challenge for DTs. In addition, to ensure acceptable palatability, DTs may require the inclusion of sweetening agents and/or flavourings with consideration that acceptable flavour profiles may be different across different geographic areas.[31,32,33,34,35,36,37,38] Due to the advantages of DTs described above, their development for and use in paediatric products in LMICs has been recommended by WHO and UNICEF.

5.1.1.2 Acceptability of dispersible tablets

Volume of dispersion and palatability are likely to be key product attributes affecting the acceptability of DTs, although ease of dosing, especially compared to crushing tablets, is also of importance. The size of particles within a dispersion can have an impact on palatability, and insoluble particles larger than approximately 250 µm have been reported to give a gritty mouthfeel and be poorly accepted.[39] Zinc dispersible tablets have been perceived as being acceptable by over 90 % of caregivers of children aged less than 5 years.[40] In addition, higher acceptability and tolerability has been reported in young children for a dispersible artemether-lumefantrine tablet compared to a dihydroartemisinin-piperaquine tablet. The dispersible tablet was considered to be simpler to use and to have a better taste.[41]

More recently, good overall acceptability was observed for a novel dispersible paediatric levofloxacin formulation in young children, being more palatable and easier to prepare than the adult product.[42] In contrast, DTs have been perceived as being liked less than chewable tablets, lozenges, or liquids, although easy to prepare.[43] Of note, participants in this study may have been influenced by previous experience with sweet oral liquids, lozenges and vitamin C tablets.

5.1.1.3 Examples of dispersible tablet technologies

DTs are commonly manufactured by direct compression, which is a relatively cheap and non-complex manufacturing process, although granulation or molding may be used. In order to ensure rapid disintegration and the production of a palatable dispersion, DTs often contain a large range of functional excipients such as fillers, lubricants, disintegrants, sweeteners, dispersion aids and flavourings. The use of co-processed excipients (combinations of two or more excipients, prepared by for example spray drying, wet granulation or co-crystallisation, to modify their physical properties), can reduce the number of excipients required and improve the manufacturability and physical properties of DTs.[44,45]

Although not a conventional dispersible tablet technology, Parvulet™ technology allows the conversion of a tablet or powder into a gel-like semi-solid through activation with water. To administer the product, the Parvulet™ tablet may be placed on a spoon and a few mL of water added to form a soft semi-solid for immediate swallowing.

FIGURE 3. Parvulet™ Technology[46]

Examples of commercially available co-processed excipients that may be used for DTs are provided in **Table 1**.

TABLE I Examples of commercially available co-processed excipients1 for DTs

Name and Company	Composition
CombiLac® (Meggle)	70 % alpha-lactose monohydrate, 20 % microcrystalline cellulose, 10 % native corn starch
F-Melt® Type C (Fuji Chemical Industries)	70 % D-mannitol, 10–25 % microcrystalline cellulose, 2–9 % xylitol, 5–13 % crospovidone, 2–9 % dibasic calcium phosphate anhydrous
F-Melt® Type M (Fuji Chemical Industries)	70 % D-mannitol, 10–25 % microcrystalline cellulose, 2–9 % xylitol, 5–13 % crospovidone, 2–9 % magnesium aluminometasilicate
Ludiflash® (BASF)	90 % D-mannitol, 5 % crospovidone, 5 % polyvinyl acetate dispersion
MicroceLac® 100 (Meggle)	75 % alpha-lactose monohydrate, 25 % microcrystalline cellulose
Pharmaburst® 500 (SPI Pharma)	85 % D-mannitol, < 10 % silicon dioxide, < 10 % sorbitol, 5 % crospovidone
SmartEx® (Shin-Etsu)	D-mannitol, polyvinyl alcohol, low-substituted hydroxypropyl cellulose

Note, these co-processed excipients may also be suitable for oro-dispersible tablets, see section 5.1.2.

[1] Co-processed excipients are combinations of two or more excipients, prepared by spray drying, wet granulation or co-crystallisation, to modify their physical properties.

5.1.1.4 Examples of marketed dispersible tablet products

Some examples of marketed dispersible products indicated for use in children are provided in **Table 2**.

TABLE 2 Examples of marketed dispersible tablet products indicated for use in children[a]

Example of Product/Brand Name	Drug(s) and Strength	Indication[b]
		CHILDREN (below 12 years)
Abacavir/lamivudine dispersible tablets	Abacavir 120 mg/Lamivudine 60 mg	Treatment of HIV-1(from 6 weeks)
Amoxicillin Dispersible tablets	Amoxicillin 250 mg and 500 mg	Pneumonia (from 2 months)
Artemether/Lumefantrine dispersible tablets	Artemether 20 mg/Lumefantrine 120 mg	Uncomplicated malaria due to Plasmodium falciparum (children 5 Kg and above; approx. 2-3 months)
Eurartesim® Dispersible tablet	piperaquine 320 mg and dihydroartemisinin 40 mg	Uncomplicated malaria due to Plasmodium falciparum (from 6 months)
Lamictal Dispersible tablets	Lamotrigine 2 mg, 5 mg, 25 mg and 100 mg	Adjunctive or monotherapy treatment of partial seizures and generalised seizures (from 2 years)
Paracetamol Dispersible tablets	Paracetamol 100 mg and 250 mg	Pain (from 6 months)
Rifampicin/Isoniazid/Pyrazinamide & Rifampicin/Isoniazid dispersible tablets	Rifampicin 75 mg, Isoniazid 50 mg, Pyrazinamide 150 mg	Capitalize Drug-sensitive tuberculosis disease (3-drug and 2-drug fixed-dose combination) and infection (2-drug fixed-dose combination) (from birth)
SPAQ-CO	Amodiaquine 150 mg Sulfadoxine-Pyrimethamine 500 mg/25 mg	Seasonal malaria chemoprevention (from 1 year)
Sulfamethoxazole/Trimethoprim Dispersible tablets (cotrimoxazole)	Sulfamethoxazole 100 mg/Trimethoprim 20 mg	Pneumocystis pneumonia, prophylaxis against infections in HIV patients (from 1 month)
Tracleer® Dispersible tablets	Bosentan 32 mg	Treatment of pulmonary arterial hypertension (from 1 year)
Ucedane® Dispersible tablets	Carglumic Acid 200 mg	Treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency (from birth)
Zinc Dispersible tablets	Zinc 20 mg (as sulfate)	Diarrhea (from 1 month)

Note, FDA may refer to dispersible tablets as Tablets for Oral Suspension.

[a]Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.1.2 Oro-dispersible tablets

Oro-dispersible tablets (ODTs), also known as fast melts, are designed to disintegrate rapidly in the mouth upon contact with saliva. Unlike DTs (see section 5.1.1), they do not require water or another beverage for administration. ODTs are often presented in blister packs.

5.1.2.1 Advantages and Disadvantages

Like DTs, ODTs are generally more stable than liquids, are less bulky and do not require preservatives, although they can be susceptible to moisture and may require moisture protective packaging. ODTs have limited dose flexibility but they are easy and convenient to take, with no manipulation or mixing with fluid required. Since the product can remain in contact with the oral mucosa for up to a minute, ODTs may require the addition of flavouring and/or sweetener to ensure acceptable taste. Other taste-masking strategies

such as the incorporation of coated drug particles can also be employed with ODTs (see also sections 5.1.3 and 5.1.7). Modified release drug particles may also be incorporated, although size needs to be kept to a minimum to reduce grittiness perception.

5.1.2.2 Acceptability of oro-dispersible tablets

Many studies investigating the acceptability and patient preference of ODTs have been conducted in adults, whilst few appear to have been reported in children. For example, ODTs have been shown to be acceptable in children from 2 years of age.[47] A survey conducted in children aged over 6 years reported that ODTs were preferred over liquids, tablets and capsules.[48] However, an investigation into healthcare professionals' opinions on ODTs showed a higher preference for liquids, followed by ODTs.[49] Mouthfeel (grittiness), taste and speed of disintegration are key ODT attributes that can affect acceptability. In addition, as with other solid oral dosage forms, dimensions (size) of the ODT may affect acceptability according to patient age. Oro-dispersible mini tablets (ODMTs) have been developed to combine the benefits of mini tablets (see section 5.1.4) with ODTs and have been clinically evaluated in paediatric patients from birth.[50,51] A study in adults suggested that ODMTs were highly acceptable and easy to take.[52]

5.1.2.3 Examples of oro-dispersible tablet technologies

ODTs are generally manufactured by direct compression, lyophilisation (freeze drying) or compression molding whilst newer technologies including mass extrusion, spray-drying and electrostatic spinning have been investigated.[53,54,55,56,57,58]

The direct compression method is considered to be the cheapest process since it involves a well-established tablet manufacturing process whereby a powder blend of drug and excipients is compressed. ODTs manufactured by direct compression often contain sugars and sugar alcohols (polyols) such as mannitol, xylitol, maltodextrin as these excipients provide good taste and mouthfeel to the product. Furthermore, co-processed excipients, including those discussed in section 5.1.1 and listed in Table 1 may be used. Lyophilized ODTs are manufactured via solvent sublimation from a frozen solution or suspension of API containing matrix forming excipients. ODTs manufactured by this process are very porous and disintegrate very rapidly in the mouth within seconds. However, they tend to be more fragile and moisture sensitive compared to ODTs manufactured via direct compression. In compression molding, a powder blend containing API and excipients is moistened with solvent and compressed into mold plates, which are then air dried.

Examples of commercially available ODT technologies are provided in **Table 3**. Some of these technologies incorporate taste-masking technologies.

TABLE 3 Examples of commercially available oro-dispersible tablet technologies

Name	Company
Zydis® (Lyophilized)	Catalent
Lyoc® (Lyophilized)	Galien LPS
QuickSolv® (Lyophilized)	Janssen Pharmaceutica
OraSolv® (Direct compression)	CIMA Laboratories Inc.
DuraSolv® (Direct compression)	CIMA Laboratories Inc.
Pharmaburst® (Direct compression)	SPI Pharma™
WOWtab® (Direct compression)	Yamanouchi Pharmaceutical Co.
Flashtab® (Direct compression)	Ethypharm SA
Advatab® (Direct compression)	Adare Pharmaceuticals

5.1.2.4 Examples of marketed oro-dispersible tablet products

Some examples of marketed oro-dispersible products are provided in **Table 4**.

TABLE 4 Examples of marketed oro-dispersible products indicated for use in children[a]

Example of Product/Brand Name	Drug and Strength	Indication[b]
		CHILDREN (below 12 years)
Calpol® Six Plus Fastmelts	Paracetamol 250 mg	Mild to moderate pain and as an antipyretic (from 6 years)
LAMICTAL ODT	Lamotrigine 25 mg, 50 mg, 100 mg and 200 mg	Adjunctive therapy for partial seizures, primary generalized tonic-clonic seizures and generalized seizures of Lennox-Gastaut syndrome (from 2 years).
Loratadine Orodispersible tablets	Loratadine 10 mg	Symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria (from 2 years)
PREVACID Solu Tab	Lansoprazole 15 mg and 30 mg	Treatment of heartburn and other symptoms associated with gastroesophageal reflux disease, healing and symptom relief of all grades of erosive esophagitis (from 1 year)
Zofran® Melt	Ondansetron 4 mg and 8 mg	Management of chemotherapy-induced nausea and vomiting (from 6 months)

[a]Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.1.3 Multi-particulates

The term multi-particulate (MP) may be used for small solid multiple-unit dosage forms which are usually from 0.05 mm (50 micron) in diameter. Commonly used descriptions for MPs include granules, pellets and beads. Mini tablets (1-3 mm in diameter) are sometimes also referred to as MPs but will discussed in section 5.1.4. MPs may be presented in unit dose packs such as sachets or capsules for opening, or in multi-dose containers.

5.1.3.1 Advantages and Disadvantages

Since MPs are solid dosage forms, they typically have superior stability compared to liquids and semi-solids and are therefore less likely to require temperature-controlled storage and transportation, thus facilitating the supply chain. In addition, the primary packaging used for MP products tends to have a smaller footprint than that of oral liquid medicines. Furthermore, they do not require preservatives to maintain microbiological quality.

MPs are versatile dosage forms that can be used for both immediate and modified drug release and may be administered to the patient in numerous ways including for example in hard gelatin capsules swallowed whole, as “sprinkles” where they are mixed in a beverage or soft food before swallowing, or via direct dosing in the mouth. If intended for mixing in a vehicle for administration, it is important that the MPs are compatible and stable within the vehicle, and that the whole dose is taken. Furthermore, MPs may be reconstituted with water to produce a suspension for administration, although this method of administration is not discussed in this document. MPs may be coated for taste-masking purposes (see section 5.1.7) or to delay drug release (see section 5.1.8).

Flexibility of dosing can be achieved through the application of different sized unit dose packs, or by administering different numbers of unit dose packs. For example, a 4-in-1 abacavir/lamivudine/lopinavir/ritonavir fixed dose combination sprinkle capsule product (under review by the FDA) containing taste-masked granules has been developed (Quadrimune) whereby dose flexibility is achieved by varying the number of capsules administered per dose.[59]

FIGURE 4 Quadrimune "4 in 1" abacavir/lamivudine/lopinavir/ritonavir sprinkle capsule (under review by FDA)[60]

Where MPs are presented in multi- dose containers (e.g. Creon®, Viread®), dose flexibility is provided through the provision of a measuring device for example a spoon or scoop for dose measurement. A new oral syringe/dispenser type delivery device has been developed to measure and dose MPs in a similar manner to oral liquids. The Sympfiny® Multi-Particulate Delivery System comprises a re-usable dispenser with an interlocking tip that automatically seals and interfaces with a specially designed bottle adaptor.[61] Although this device may enable the accurate easy measurement and dosing of MPs, it has not yet been commercialised and cost may potentially be prohibitive for low resource settings.

FIGURE 5 Sympfiny® Multi-Particulate Delivery System[62]

The X Straw® device has been developed by DS Technology for dosing MPs. The straw is filled with a pre-measured dosage of drug pellets or granules and has a special control filter at one end and a cap at the other. The patient dips the straw into a beverage of choice, removes the cap and sucks like a conventional drinking straw. During the drinking process, the filter moves up the straw and pushes the granules upwards which are then swallowed by the patient with the beverage.

MPs may also be incorporated into other dosage forms such as compressed tablets,[63,64,65,66] oro-dispersible tablets[67] and dispersible tablets.[68]

5.1.3.2 Acceptability of multi-particulates

Due to the small dimensions of MPs they are easy to swallow and are generally considered to be acceptable for infants after weaning (from approximately 6 months of age), although they may also be suitable for younger infants and neonates if administered in a liquid vehicle.[69] MPs have been reported to be well accepted in children and to be preferable to a dispersed formulation or oral liquid.[70,71] It should however be noted that particle size, as well as shape, texture, hardness, taste and dose volume (amount) may be critical to MP acceptability.[72] Studies investigating the palatability and acceptability of various quantities of different sizes of MPs in adults administered in vehicles of different viscosities concluded that grittiness scores increased with increasing MP size and dose, whilst grittiness scores were shown to decrease with increasing vehicle viscosity. However very high viscosity vehicles were less preferred. Amount (dose) of MPs appeared to be the most significant factor regarding grittiness perception, followed by MP size.[73,74] The findings of a study in adults and children > 4 years suggest that although subjects were able to swallow the MPs, gritty mouthfeel may be a barrier to patient acceptability.[75] In the LOLIPOP trial of Lopinavir/Ritonavir (40/10mg pellets) plus dual Abacavir/Lamivudine (60/30mg tablets) in HIV infected children, one of the secondary objective was to assess the factors such as palatability that contribute to acceptability of the new 4-in-1 formulation which is now under FDA review. This study once published will provide additional data on acceptability for MPs.[76]

5.1.3.3 Examples of multi-particulate technologies

Commonly used technologies for the manufacture of MPs include extrusion spheronisation, fluid bed granulation (spray agglomeration), hot melt extrusion, drug layering, spray drying, solvent evaporation and spray congealing.[77,78,79,80,81,82] The selection of technology applied depends on several factors including physico-chemical properties of the drug, required dose range and company technical capabilities.

During extrusion spheronisation, a powder blend is mixed with granulating fluid to form a plastic mass of material, which is then extruded under pressure through an orifice to produce extrudates. These are broken into uniform lengths and gradually transformed into spheres during spheronisation. Fluid bed granulation involves the fluidisation of a powder onto which binder solution is sprayed to form agglomerates which are then dried. The production of MPs via drug layering is through the deposition of successive layers of drug on pre-formed particles, whilst during spray drying, a drug solution or suspension is atomized and passed through a hot gas stream resulting in the evaporation of the liquid. The fluidised bed drug layering and coating of small MPs can be challenging due to agglomeration of the particles leading to incomplete and inconsistent coating and low yields. The process has recently been modified and optimised enabling the efficient coating of small particles from approximately 100 µm in diameter (MicroCoat™).[83] In spray congealing, drug is dissolved or dispersed in a molten carrier (e.g. lipid-based excipients), which is atomized into small

droplets and then cooled to form small particles. Spray congealed particles may have taste-masked and/or delayed release properties, depending on the lipidic excipients used. In addition, spray congealing can be used to improve bioavailability of poorly soluble drugs (see section 5.5.1).

Examples of commercially available MP technologies are provided in **Table 5**.

TABLE 5 Examples of commercially available multi-particulate technologies

Name	Company
Complex Perfect Spheres (CPS™) Technology	Glatt GmbH
Micro Pelletising (Micro Px™) Technology	Glatt GmbH
Orbexa™	Adare Pharmaceuticals
Precision Particle Fabrication®	Orbis Biosciences
MicroCoat™	Fluid Pharma

5.1.3.4 Examples of marketed multi-particulate products

Some examples of marketed multi-particulate products indicated for use in children are provided in **Table 6**.

FIGURE 6 Placebo multi-particulates in a capsule[84]

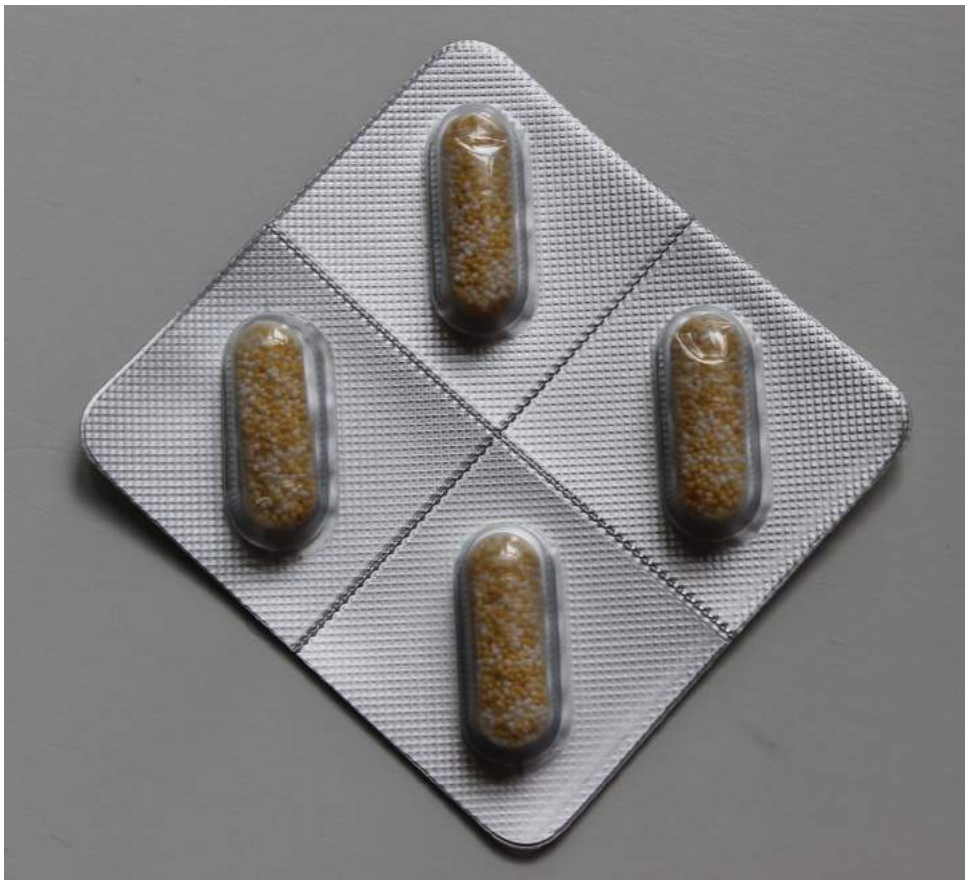


TABLE 6 Examples of marketed multi-particulate products indicated for use in children[a]

Example of Product/Brand Name	Drug and Strength	Indication[b]
		CHILDREN (below 12 years)
Creon® Micro Pancreatin gastro-resistant granules	Pancreatin 60.12 mg (per 100 mg/ scoop)	Treatment of pancreatic exocrine insufficiency (from 1 month)
Depakote® sprinkle capsules	Divalproex sodium equivalent to 125 mg of valproic acid	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures and simple and complex absence seizures (from 10 years)
Hidrasec® granules for oral suspension	Racecadotril 10 mg and 30 mg (per sachet)	Complementary symptomatic treatment of acute diarrhoea (from 3 months)
Jadenu® sprinkle	Deferasirox 90 mg, 180 mg, 360 mg (per sachet)	Chronic iron overload and thalassemia (from 2 years)
Mylanâ LPV/r granules	Lopinavir 40 mg and Ritonavir 10mg	Treatment of HIV-1 infection (from 3 months)
Nexium® gastro-resistant granules for oral suspension	Esomeprazole (as magnesium trihydrate) 10 mg (per sachet)	Gastroesophageal reflux disease (from 1 year)
PENTASA® prolonged release granules	Mesalazine 1 g, 2 g and 4 g (per sachet)	Mild to moderate ulcerative colitis (from 6 years)
Pyramax® granules for oral suspension	Artesunate 60 mg and Pyronaridine (phosphate) 180 mg	Uncomplicated P. falciparum and P. vivax malaria (children/infants between 5 and 20 kg, approx. 2-3 months)
REYATAZ® hard capsules	Atazanavir 300 mg	Antiviral combination treatment of HIV-1 (from 6 years)
Salofalk® gastro-resistant prolonged release granules	Mesalazine 500 mg, 1 g, 1.5 g, and 3 g (per sachet)	Acute episodes and the maintenance of remission of ulcerative colitis (from 6 years)
Tasigna® hard capsules	Nilotinib (as hydrochloride monohydrate) 50 mg, 150 mg, 200 mg	Philadelphia chromosome positive chronic myelogenous leukaemia (from 2 years)
Translarna® granules for oral suspension	Ataluren 125 mg, 250 mg and 1000 mg (per sachet)	Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (from 2 years)

Excludes granule products intended to be reconstituted in a bottle to produce a multi-dose pack oral liquid suspension.

[a]Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.1.4 Mini tablets

Mini tablets are compressed tablets with a diameter of 1-3 mm, although the term “mini tablet” has also been used for tablets 4 mm in diameter. As stated above, mini tablets may be referred to as sprinkles or granules and are often filled into capsules and sachets.

FIGURE 7 Placebo mini tablets[85]

5.1.4.1 Advantages and Disadvantages

Unsurprisingly mini tablets have many of the advantages of MPs described above: good stability properties, suitable for immediate and modified release, and flexibility of dosing through the use of different unit dose pack sizes. In addition, mini tablets may also be dosed as a single or a small multiple number of mini tablets per dose (e.g. up to 5) for potent/ low dose drugs, although there do not appear to be any commercialised mini tablet products using this approach yet. One key challenge is the current lack of commercially available mini tablet counting or administration devices. For those that are available, the costs and the possibility of breakage, loss, or becoming unhygienic may present challenges in their use. However, several approaches are under development and it is anticipated that devices will become available in the near future. For example, Philips-Medisize is planning to commercialise its Mini Tablet Dispenser in 2020.[86] This device is mounted on top of a standard tablet bottle and is designed to allow a patient or caregiver to count and dispense mini tablets in predetermined amounts from one to twenty tablets. Balda have developed a Smart Mini Tablet Dispenser (sMTS) for counting and dispensing mini tablets that can be modified according to the product.[87]

FIGURE 8 Balda Smart Mini Tablet Dispenser[88]

Another advantage of mini tablets is that they can be manufactured using similar processes and unit operations to traditional conventional sized tablets, although multiple tip tooling is required. Hence it may be possible to utilise already developed tablet formulations and therefore expedite paediatric formulation development. However, drug loading per mini tablet is generally low and good powder flow properties and narrow particle size distribution are required to ensure successful manufacture and acceptable drug content uniformity.[89,90,91,92,93]

5.1.4.2 Acceptability of mini tablets

Several studies have shown the swallowability and acceptability of mini tablets in children. As stated above, mini tablets are considered to be ≤ 3 mm in diameter, however 4 mm "mini tablets" have been reported to be well accepted in children aged 1-4 years.[94] Single mini tablets 3 mm in diameter have been shown to be safe for use in children aged from 2 years ,[95] whilst single uncoated 2 mm diameter mini tablets have been shown to be as well accepted as 0.5 mL syrup in neonates.[96] Interestingly, uncoated mini tablets appear to be better accepted than syrup in older children from 6 months of age, although if coated, mini tablets may be more appropriate for children aged 1 year and above.[97] It should be noted however that young children may chew mini tablets and therefore break the integrity of any coatings. Multiple (5 or 10) 2- and 3-mm mini tablets in jelly have been shown to be easily swallowed and well tolerated in 2 and 3 year olds[98,99] whilst ≥25 x 2 mm uncoated mini tablets administered with a drink appear to be well tolerated by children from 6 months of age.[100] In addition, mini tablets as "sprinkles" mixed with food or breast milk have been found to be preferable for infants and young children compared to a syrup, although this may have been in part due to ease of transportation and storage. In contrast, older children preferred a tablet formulation. In contrast, older children preferred a tablet formulation.[101] A study in adults suggested that less than5 mini tablets of 3 mm diameter are preferred to 10 mini tablets of the same size. Emerging research suggests that the acceptability of a 2.5 x 6 mm oblong tablet is comparable to the acceptability of three 2 x 2 mm mini tablets, and higher than that of 3 mL syrup in children aged 1 to 6 years.[102]

5.1.4.3 Examples of mini tablet technologies

Mini tablets are developed and manufactured in a similar manner to conventional sized tablets for example using direct compression, wet granulation or dry granulation, depending on the properties of the drug. As noted above, due to the small size of the tablets, stringent controls on the physical properties of the raw materials and powder blend are required to ensure acceptable drug content uniformity.

5.1.4.4 Examples of marketed mini tablet products

Some examples of marketed mini tablet products indicated for use in children are provided in **Table 7**.

TABLE 7 Examples of marketed mini tablet products indicated for use in children[a]

Example of Product/Brand Name	Drug and Strength	Indicationb
		CHILDREN (below 12 years)
Desitrend® coated mini-tablets	Levetiracetam 250 mg, 500 mg and 1000 mg (per sachet)	Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy (from 1 month)
Lamisil® oral mini-tablets	Terbinafine hydrochloride 125 mg and 187.5 mg (per sachet)	Treatment of tinea capitis (from 4 years)
LPV/r pellets	Lopinavir 40 mg and ritonavir 10 mg (per capsule)	Treatment of HIV-1 infection (from 3 months)
Orfiril® Long mini-tablets	Sodium valproate 500 mg and 1000 mg (per sachet)	Generalized seizures and partial seizures in epilepsy (from 10 years)

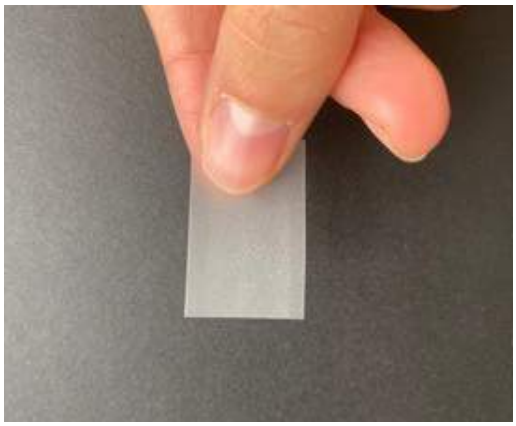
[a]Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.1.5 Oral films

Oral films may be buccal or oro-dispersible and are administered without the need for water. They are typically the size of a postage stamp and usually comprise a film forming polymer which acts as a carrier matrix with drug and other excipients such as plasticizers to ensure film flexibility and flavours/sweeteners to improve palatability. Buccal films are mucoadhesive and can be attached to the oral mucosa where they release drug for local or systemic delivery. Oro-dispersible films are designed to rapidly dissolve or disperse in the mouth for systemic drug delivery.

FIGURE 9 Placebo oro-dispersible film [103]



5.1.5.1 Advantages and Disadvantages

Oral films can be easily administered without the need for water and are portable, although they are unstable in humid environments and therefore require moisture protective packaging. The development of oral film medicinal products is relatively new compared to other more traditional oral dosage forms and therefore manufacturing may require dedicated facilities and therefore be more expensive. Indeed, many patents exist, and new product developments may require to be conducted through partnerships. Flexibility of dosing can be achieved through the administration of different sized films and the concept of personalised dosing has been proposed whereby different lengths of film containing drug or different quantities of drug are printed onto a film according to patient needs.[104,105] Research into devices for measuring and dispensing oral films is on-going.[106] High drug loading for inkjet-printed films can be challenging, especially for low solubility drugs, although printing multiple layers may be possible.[107] Potential drug loading within oral films is also limited; up to approximately 30 % w/w may be incorporated before the properties of the film are adversely affected. Therefore, this dosage form is only suitable for high potency drugs. Oral films generally require the inclusion of a flavour and/or sweetener to ensure acceptable palatability. In addition, as with ODTs, taste-masked and/or modified release drug particles may be incorporated into oral films. Modified release properties may also be achieved by using multi-layered films, an approach which is also amenable to delivery of fixed dose drug combinations. Since drug absorption through the buccal mucosa avoids gastrointestinal absorption, buccal films can be used to systemically deliver drugs that are susceptible to degradation in the stomach, and also avoid hepatic first pass metabolism. Indeed, such films could potentially be used for the delivery of proteins and vaccines.

5.1.5.2 Acceptability of oral films

Appearance, pH, mouthfeel, size (including thickness) and taste are important attributes for oral film acceptability. In addition, perceived stickiness and disintegration in the mouth

can influence acceptability.[108] Oro-dispersible films up to 350 µm and 2x3 cm^2 in size are considered to be acceptable, whilst smaller sized mucoadhesive films (1-2 cm^2) may be preferred.[109] Ease of taking an oral film and been found by adults to be significantly higher than a tablet, although taste appeared to be similar.[110] A 2x3 cm^2 oro-dispersible film has been found to be acceptable in young children aged from 6 months to 5 years and their caregivers. Acceptability was reported to be especially high in those aged 3 years and above. However, although the majority of subjects swallowed the film, sticking to the teeth, lips or palate resulting in partial spitting out was noted in 15 % of subjects.[111] Non-inferiority of the acceptability of a 2x3 cm^2 oro-dispersible film compared to 0.5 – 3 mL syrup has been reported in neonates and infants aged 2 days to 12 months, with overall superior swallowability of the film.[112]

5.1.5.3 Examples of oral film technologies

Oral films may be manufactured by solvent casting, hot melt extrusion and printing of drug onto film via inkjet or flexography. Solvent casting is the most common and cheapest technique for film manufacture. The film ingredients are mixed or dissolved in an aqueous or hydroalcoholic solvent and the resulting liquid casted onto a surface, e.g. petri dish or liner, dried and cut. Both non-continuous and continuous film manufacturing machines are available. Films can also be manufactured by hot melt extrusion whereby polymer, drug and other excipients are melted, extruded and shaped into a film followed by cooling. During electrospinning, the formulation is pumped through a needle with a controlled flow and charged under a high voltage electric current above an opposite charged collector, producing a highly porous oro-dispersible film. Ink printing technologies for depositing defined doses of drug onto films are gaining interest. For example, flexographic printing which is an off-set rotary printing process allows the printing of drug loaded suspensions and solutions onto oral films. Another printing technique is ink jet printing which enables the digitally controlled formation and placement of small liquid drops of ink (containing drug) onto a substrate, and may be used for multiple drugs.[113,114,115,116,117,118,119,120,121,122,123,124,125,126] As mentioned in section 5.1.5.2., multi-layer films may be developed and manufactured to modify drug release. For example, for local therapy, a dissolvable drug matrix film layer can be coated with a mucoadhesive film layer as the mucosal contact layer, allowing drug release into the oral cavity. Conversely, a backing layer may be added to shield the drug layer from the oral cavity thus promoting systemic delivery via transmucosal permeation.[127]

Examples of commercially available oral film technologies are provided in **Table 8**.

TABLE 8 Examples of commercially available oral film technologies

Name	Company
PharmFilm® (buccal and oro-dispersible)	Aquestive Therapeutics
Rapidfilm® (oro-dispersible)	tesa Labtec
VersaFilm® (buccal and oro-dispersible)	IntelGenx Corp.
BEMA® (buccal)	BioDelivery Sciences
BIO-FX™ (oro-dispersible)	NAL Pharma

AdHex Pharma and LTS Lohmann Therapie-Systeme AG also provide oral film development services.

5.1.5.4 Examples of marketed oral film products

Some examples of marketed oral film products are provided in **Table 9**.

TABLE 9 Examples of marketed oral film products indicated for children and adolescents[a]

Example of Product/Brand Name	Drug and Strength	Indication[b]
		CHILDREN (below 12 years)
Setofilm® (dispersible) ZUPLENZ® (dispersible)	Ondansetron 4 mg and 8 mg	Management of chemotherapy-induced nausea and vomiting (from 6 months), prophylaxis and treatment of post-operative nausea and vomiting (from 4 years)
		ADULTS and Adolescents (12 - <18 years)
EXSERVAN™ (dispersible)	Riluzole 50 mg	Amyotrophic lateral sclerosis (adults only)
SUBOXONE® (buccal)	Buprenorphine 2 mg, Naloxone 0.5 mg and 4 mg/1 mg, 8 mg/2 mg and 12 mg/3 mg	Opioid Substitution Therapy (adults only)
BELBUCA™ (buccal)	Buprenorphine 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg	Management of severe pain (adults only)

[a]Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.1.6 Novel oral delivery systems for biologic drugs

Biologic drugs, for example hormones, monoclonal antibodies and nucleic acid, cannot be administered orally as they are prone to degradation in the GI tract and are not readily absorbed. They are therefore generally administered via injection. To overcome this issue, several novel oral drug delivery systems are being developed. For example, an indigestible capsule coated with pH sensitive polymer containing dissolvable drug-containing microneedles is being evaluated. Following ingestion and upon reaching the small intestine, the capsule is designed to release and propel the microneedles into the intestinal wall, thus delivering the drug.[128,129] The RaniPill™ capsule has also been developed to pass through the stomach and deliver drug to the intestinal wall. When the capsule reaches the intestine, it is activated, and a balloon mechanism pushes microneedles containing the drug into the intestinal wall.[130] Both technologies are at an early stage of development and may be applicable to adolescents but would require further modification (e.g. size reduction) and safety assessment for use in younger patients.

5.1.7 Taste-masking technologies

The taste of a formulation has a significant impact on the palatability of a product, which may be defined as the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth).[131] Aversive or unpleasant taste has been a commonly reported barrier to oral medicine compliance in children.[132,133] Therefore, the application of taste-masking technologies to ensure acceptable palatability and facilitate medication adherence is of key importance for paediatric medicines. It should be noted that caregivers may mix a medicine with food or beverage to improve its taste, although this should be discouraged unless the co-administration with defined foods/beverages has been evaluated and recommended to facilitate medicine administration (for example MPs).

The mechanism of taste is complex and an area of on-going research. The taste bud is the principal sensory organ of gustation and is composed of groups of between 50 and 100 taste receptor cells, with a network of sensory nerves. When taste cells are stimulated by chemicals binding to their receptors, they depolarize, and this depolarization is transmitted to the taste nerve fibres resulting in an action potential that is ultimately transmitted to the brain. Chemical stimuli, including drugs, must be in solution to reach and stimulate the receptor cells.[134] Various taste masking strategies have been developed to reduce, prevent or block the stimulation of bitter taste receptors and/or the perception of bitterness.

The most commonly used approach for taste-masking oral medicines is the use of sweeteners and/or flavourings, although a "trial and error" technique to determine optimal type and concentration is often needed. Sweeteners may be classified as bulk (sugar alcohols, e.g., sorbitol, mannitol, xylitol) or intense (many times sweeter than sugar, e.g., saccharin, aspartame and acesulfame K (ace K)) and a combination of more than one sweetener may be required. In addition, some sweetener combinations have synergistic activity, for example aspartame with acesulfame potassium. It has recently been reported that cyclamate can inhibit the two human bitter taste receptors responsible for the bitter after-taste of saccharin, and similarly that saccharin can supress the responses of the bitter receptor to cyclamate. Hence mixtures of these two intense sweeteners may decrease some of the bitterness associated with their use. Flavourings are complex mixtures and can be natural or artificial. Selection may be based on several factors including compatibility with the formulation, regulatory acceptability and taste characteristics of the drug. Flavour preferences may vary according to geography and culture and therefore a "taste neutral" product may be preferred to avoid specific flavour recognition and preferences.

As discussed above, since a drug must be in solution to stimulate taste receptors, the intensity of a drug's aversive taste may be reduced by modifying its solubility. However, if such an approach is used, the impact on bioavailability must be considered. For example, the pH of the formulation may be adjusted such that the drug is insoluble in the mouth when ingested. Other approaches include use of a different drug salt, a pro-drug or co-crystal.

Barrier techniques such as complexation or coating may be used to provide taste-masking. Ion exchange resins (IERs) are water insoluble polymers containing acidic or basic functional groups which are able to reversibly exchange counter ions in aqueous media. Drug-IER complexes are designed only to dissociate when in the GI tract. Cyclodextrins are cyclic oligosaccharides that can interact with a variety of molecules whereby whole or part of the guest molecule fits into the cyclodextrin cavity. In addition to providing taste masking, cyclodextrins can increase the bioavailability (see section 5.5.1) and stability of drugs.

Various technologies may be used to apply a physical barrier to a drug or dosage form. Polymer film coating is a well-recognised technique for taste masking oral solid dosage forms such as tablets, capsules and multi-particulates. pH sensitive polymers that remain intact within the oral cavity may be used as well as combinations of water insoluble and water-soluble polymers. Furthermore, lipid-based excipient coatings can be used for taste-masking. Coatings may be applied to dosage forms by fluidised bed or drum coating systems, whilst approaches for coating drug particles include microencapsulation and coacervation. The embedding of drug particles within a polymer or lipid matrix (solid dispersion) may also provide taste-masking, for example by using technologies such as hot melt extrusion, spray drying or spray congealing.[135,136,137,138,139,140,141,142,143]

TABLE 10 Examples of commercially available taste-masking technologies

Name	Company
Microcaps® (encapsulation)	Adare Pharmaceuticals
Opadry® (polymer coating)	Colorcon
OXPZero™	Oxford Pharmascience
Actimask®	SPI Pharma
Formulcoat® (coating)	Pierre Fabre Medicament

Nanohybrid technology has been used for taste masking whereby nano-ordered composite materials consisting of drug and inorganic materials such as silica, bentonite and alumina are utilised.[144] The excipient Kleptose® Linecaps is reported to have taste-masking properties. This consists of spray dried high amylose content pea maltodextrin (40 % amylose, 60 % glucose, oligosaccharides and polysaccharides). In water, linear amylose molecules can form helical structures with an inner hydrophobic cavity. Taste masking may be achieved through drug molecules becoming trapped within the coiled amylose chains.[145]

The concept of bitter blockers to improve the palatability of a product is a growing area of interest. At least 25 different bitter taste receptors have been discovered in humans and bitter receptor antagonists ("bitter blockers") bind competitively to a specific bitter receptor. Bitter blockers are only successful for taste masking if the bitter drug molecule and bitter blocker bind to exactly the same receptor. Examples of bitter blockers include adenosine 5-monophosphate, neohesperidin dihydrochalcone, thaumatin, and sodium salts such as sodium gluconate and monosodium glutamate. In addition to being compound specific, the effectiveness of bitter blockers can vary with age of the taster.[146,147,148]

A recent collaboration between Discovery BioMed Inc. and the Monell Chemical Senses Center is seeking to identify GRAS (generally recognized as safe) materials that can block the off-tastes of life-saving oral medicines (artemisinin, piperaquine, praziquantel and zinc sulfate), to facilitate compliance in paediatric patients. Several stages are involved in the project as follows:

- Human studies will be conducted to determine the oro-sensory and nausea-inducing profiles of the selected drugs.
- Cultured human taste cells will be used to identify if bitter, sour or other taste cell types are stimulated by the drugs.
- Those of the 25 different human bitter receptors are activated by the drugs will be identified.
- Sensory cells that respond positively to the drugs will be used to identify potential receptor blockers, via high-throughput screening assays of compounds.
- Compounds identified as potential blockers will be validated *in vitro* using cultured human taste cells and bitter receptors, and *in vivo* by human sensory testing.

5.1.8 Long-acting technologies for the oral route

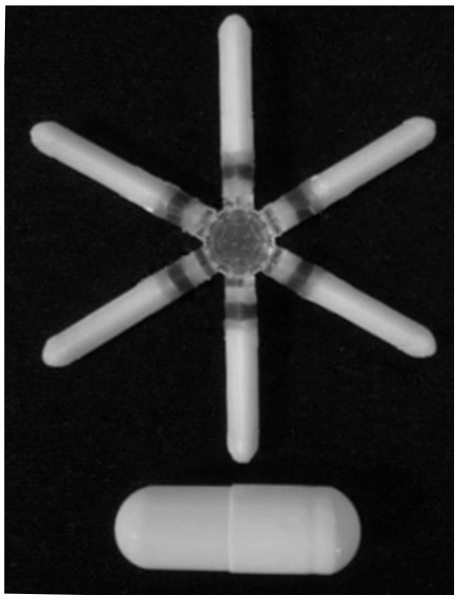
There are broadly three commonly used approaches for controlling/sustaining drug release from solid oral dosage forms such as tablets, mini tablets, MPs and buccal films. Furthermore, as previously discussed, controlled release MPs may be incorporated in oro-dispersible formulations and powder/granules for constitution into liquids. In matrix systems, drug is encapsulated or dispersed in a polymeric and/or lipidic matrix. Hydrophilic polymers swell in contact with aqueous medium to form a gel and the drug is slowly released via dissolution, diffusion or erosion. In reservoir matrix systems drug particles or dosage forms are coated with a polymer or lipidic membrane that controls drug release rate from the inner matrix. Oral osmotic pump systems operate on osmotic pressure and tend to be applicable for monolithic dosage forms (including implants, see section 5.3.3.2). A core comprising two compartments is surrounded by a semi permeable membrane coating which has an orifice. One compartment contains drug and the other contains an osmotic agent. Fluid enters the dosage form through the semi-permeable membrane and the drug dissolves or becomes suspended. The resulting increase in osmotic pressure causes the drug to be pumped out of the orifice, the rate of which is controlled by the size of the orifice and thickness of the membrane. A combination of approaches may be used and with all polymeric systems, the rate and location within the gastro-intestinal (GI) tract of drug release can be modified according to the properties of the polymer(s). For example, enteric polymers are insoluble in low pHs and hence drug release only occurs in the higher pHs of the small intestine.[149,150,151,152,153,154,155,156,157]

It should be noted that the use of polymers to control or sustain drug release, for example mucoadhesives and hydrogels, can be applied to non-oral routes of administration including the parenteral, rectal, vaginal, nasal and ophthalmic routes.[158] However, the focus of research in this area appears to be for adults.

Gastro retentive oral dosage forms are designed to stay in stomach for longer than normal to maximise drug absorption in the proximal GIT. Mechanisms through which this may be achieved include floating systems, expandable systems, high density systems and mucoadhesive systems. For example, the inclusion of a highly porous layer or a swellable system can be used to ensure the floating of the dosage form on top of the gastric contents, and iron oxide can be incorporated to increase the density of the formulation to increase gastric retention. In addition, the geometry and shape of the dosage form can be modified to optimise retention time and drug release.[159,160,161,162]

A long acting gastro-retentive capsule (Lyndra capsule)[163] has been recently developed that to deliver drug for a week or more. Within the capsule is a folded star-shaped drug containing element. There is a central “core”, drug-containing “arms” radiating from the core delivering controlled drug release and disintegrating matrices that join the arms to the core. The capsule dissolves in the stomach and the dosage form unfolds. The drug containing element remains in the stomach and starts to deliver drug to the patient. The disintegrating matrices break down after approximately 7 days and are eliminated via passage through the lower GI tract.[164] This is an emerging technology, being investigated for its use in HIV or malaria with support from BMGF. Its application to children is not foreseen in the near future.

FIGURE 10 Lyndra® long-acting gastro-retentive capsule[165]



5.2 Rectal route dosage forms

Drug delivery via the rectum may be a useful alternative route to the oral route and unlike injections, does not require administration by a healthcare professional. Examples of rectal dosage forms include liquids (solutions, suspensions or emulsions), semi-solids such as gels, foams, creams and ointments, and solids such as tablets, capsules and powders for reconstitution, and suppositories. The latter appear to be the most commonly available rectal dosage form and are discussed in greater detail below. It should be noted that some of the described advantages and disadvantages of suppositories may also apply to other rectal dosage forms.

5.2.1 Suppositories

Suppositories are single unit solid dosage forms that contain drug solubilised or dispersed in a suppository base. Once inserted in the rectum, drug is released via melting or solubilisation, where it is absorbed by the transcellular and paracellular routes. Suppositories can be used for both local and systemic treatments, the most common being for constipation, analgesia, anti-pyrexia, anti-inflammatory and anti-emesis. In addition, there is growing interest in the use of suppositories for anti-biotics, anti-malarials and anti-HIV microbicides, and indeed rectal artesunate for malaria is currently available and being scaled-up through the Unitaid-funded CARAMAL project lead by the Clinton Health Access Initiative (CHAI).[166,167,168,169,170]

5.2.1.1 Advantages and Disadvantages

Unlike oral drug delivery, suppositories may be used to administer drugs to unconscious or vomiting patients as well as those who have difficulty in swallowing tablets and capsules, for example geriatric and paediatric patients. Suppositories can be used to avoid local gastric irritation and proteolytic enzymes, and taste-masking of aversive tasting drugs is not required. In addition, drug administration via the rectal route can avoid or minimise hepatic first pass metabolism: the lower rectum is drained by the lower (inferior) and middle haemorrhoidal veins directly into the systemic venous circulation thereby avoiding the liver. Although suppositories can be self-administered by the patient or caregiver, it should be noted that correct positioning is important since insertion into the upper rectum

may result in drug absorption into the upper (superior) haemorrhoidal vein which drains into the portal circulation, leading to metabolism in the liver. In addition, the presence of material in the rectum and/or early expulsion of the suppository can lead to incomplete or erratic drug absorption. Suppositories offer limited flexibility of dosing, although dividable stick-shaped suppositories have been developed. The dimensions of suppositories for paediatric use are an important consideration and should not cause discomfort to the patient; rectal dimensions according to age have been estimated to be 3.0 x 6.0 cm for a 3-month-old and 3.5 x 7.0 cm for a 1 year old. Indeed, it has been reported that suppositories should not be used in neonates due to the risk of mucosal damage which may potentially result in infection. The excipients used in suppositories generally have a good safety profile. However, suppositories can melt at temperatures above 30 °C and therefore may require a temperature-controlled supply chain. In addition, glycerol-gelatin based suppositories can absorb moisture and therefore require moisture protective packaging.[171,172,173,174,175,176]

5.2.1.2 Acceptability of suppositories

Limited data are available on the acceptability of suppositories although it is recognised that this may be influenced by geographical and cultural attitudes, and discomfort. Relatively good acceptability of the rectal route for pre-school children compared to the oral route has been reported by parents in Italy, Canada, Switzerland, whilst in contrast, a study in the UK reported the rectal route to be the most unpopular compared to oral delivery or injections.[177] Rectal drug delivery is anticipated not to be preferred by older children and adolescents, which may be due to for example lack of knowledge and perceived potential for misuse.[178,179,180] There has been some documented acceptability issues with healthcare workers with the different types of formulations for suppositories which may affect their utilization.

5.2.1.3 Examples of Suppository Technologies

Suppositories are primarily manufactured using a moulding method whereby the base is heated to above the melting temperature and the drug is dispersed or dissolved in the heated liquid prior to it being dispensed into suppository moulds. There are broadly two types of suppository base, lipophilic and hydrophilic, the selection of which will depend on the properties of the drug to be administered. Lipophilic bases include excipients such as cocoa butter, hydrogenated vegetable oil and hard fats, and are designed to melt within the rectum to release the drug. Hydrophilic bases dissolve in the rectal fluids to release drug and contain glycerol, gelatine or high molecular weight polyethylene glycols. It is possible to incorporate other excipients into the suppository to modify drug release. For example, the inclusion of mucoadhesive polymers can prolong drug release rate by increasing residence time in the rectum. The use of thermo-responsive liquid suppositories has also been investigated, where the product is administered as a liquid but gels at body temperature to form a solid. Bioavailability and absorption enhancing technologies may also be applied to suppositories, for example the use of surfactants, drug nanoparticles and solid dispersions (see section 5.5.1). Hollow-type suppositories contain a hollow cavity that can be filled with solid, liquid or gel. Since both the cavity and shell can contain drug, it is possible to deliver drug combinations and potentially modify the release of each. In addition, due to the manufacturing process, it is possible to incorporate thermo-labile drugs into the cavity. Dimple type suppositories where drugs (e.g. peptides) can be embedded into the dimples on the surface have also been investigated.[181,182] Other solid rectal dosage forms under development include fast dissolving inserts[183] and recto-dispersible tablets.[184]

5.2.1.4 Examples of marketed suppository products

Some examples of marketed suppository products indicated for children are provided in **Table 12**.

TABLE 12 Examples of marketed suppository products indicated for children[a]

Example of Product/Brand Name	Drug and Strength	Indication[b]
		CHILDREN (below 12 years)
Artecap® suppositories Artesunate suppositories/ Rectocaps	Artesunate 100 mg	Pre-referral treatment for severe malaria, or as emergency treatment when oral or injectable treatment not possible (from 2 months).
Flagyl® suppositories	Metronidazole, 500 mg and 1000 mg	Anaerobic bacterial infections (from 1 month)
Glycerin suppositories	Glycerol 1 g, 2 g and 4 g	Relief of occasional constipation (from 1 month)
Nurofen for Children® suppositories	Ibuprofen 60 mg	Relief of pain and fever (from 3 months)
Paracetamol suppositories	Paracetamol 60 mg, 125 mg, 250 mg, 500 mg and 1000 mg	Treatment of mild to moderate pain and fever (from 3 months)
Prednisolone suppositories	Prednisolone 5 mg	Treatment of haemorrhagic and granular proctitis and the anal complications of Crohn's disease (No lower age limited specified)
Voltarol® suppositories	Diclofenac sodium 25 mg, 50 mg and 100 mg	Juvenile chronic arthritis (from 1 year) and for the relief of acute post-operative pain (from 6 years).

[a] Minimum age provided for lowest product strength.

[b] Indication is given based on product inserts, international recommendations, or other official information although this information may vary dependent on region and/or authorising regulatory authority.

5.3 Parenteral route dosage forms

Parenteral administration of drugs involves their injection in the form of solutions (aqueous or oil-based), suspensions (aqueous or oil-based) or emulsions. Selection of parenteral formulation will depend on the properties of the drug, required doses and intended route. Parenterals may be defined as either large-volume or small-volume. The three most common and well-established routes are the intravenous (IV), intramuscular (IM) and subcutaneous (SC) routes. IV delivery involves the administration of the formulation into a vein and usually results in a rapid response and 100 % bioavailability. Large (up to 500 mL) and small (up to 10 mL) volume formulations may be administered via this route. However, in addition to aspects such as pH and osmolarity, in paediatric patients both the volume and rate of administration need to be carefully controlled to avoid fluid overload. IM delivery involves administration into a muscle and can be used for controlled-release formulations. Normally IM volumes in children should not exceed 1 mL although smaller volumes may be required for infants and neonates. Similarly, volumes of SC injections which are administered into the subcutaneous tissue should not exceed 1 mL in paediatrics.[185] Miscellaneous routes of parenteral administration include the intra-dermal, intra-arterial and intrathecal routes.

ENHANZE® Drug Delivery Technology has been developed to allow for increased dispersion and absorption of therapies administered subcutaneously. It is based on a recombinant human hyaluronidase PH20 enzyme, which locally degrades hyaluronan in the SC space, allowing larger volumes to be delivered in a single SC injection. Therefore, some biologics and small molecule drugs may be administered SC instead of via IV infusion.[186] The suitability of this technology in paediatric patients is not known.

5.3.1 Advantages and Disadvantages

A key advantage of parenteral formulations is their ability to provide an immediate response (usually by the IV route) in acute medical situations. In addition, they can be used to ensure sufficient bioavailability of drugs that are degraded in the GI tract, for example hormones, and can be administered to patients unable to take drugs orally, for example unconscious patients. It is possible to modify drug release rate using different formulation approaches: generally, IV solutions provide immediate release whilst IM or SC formulations may be longer acting.

Parenteral formulations are sterile and therefore require specialist manufacturing facilities and processes which can be expensive. Although some patients may be able to self-administer SC injections, trained healthcare professionals are usually required for the administration of IV and IM injections. Parenteral formulations offer flexibility of dosing through the measurement and administration of different volumes however special care is needed when dosing paediatrics where small volumes and/or dilution may be required. Administration via needle can cause pain, which can be a major barrier to patient compliance, especially in paediatric patients. In addition, used needles ("sharps") must be safety disposed of. Since liquid parenteral products are generally less stable than solids, they may require a temperature-controlled supply chain. This may be mitigated by the formulation and use of lyophilized/powder injection products, although these require reconstitution with a sterile liquid (e.g. Water for Injection) before administration.

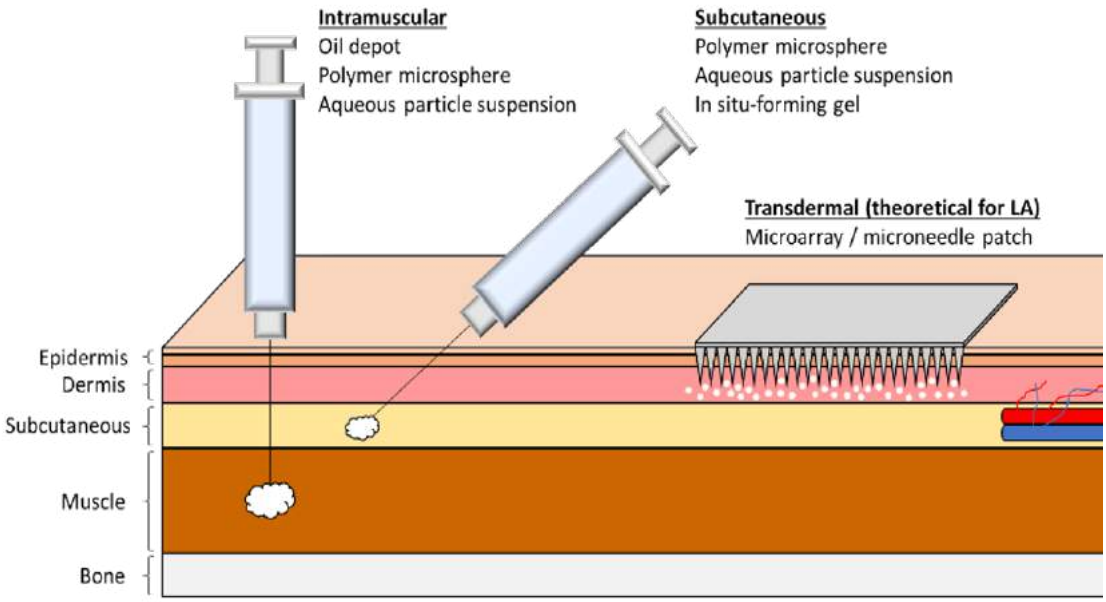
5.3.2 Acceptability of parenteral products

Although parenteral products have well-established use, few studies investigating their acceptability in paediatric patients appear to have been published. As stated above, a key barrier to parenteral products in children is pain on injection. Indeed, numerous studies have investigated fear and pain associated with needles (and other procedures) and potential intervention strategies for mitigation.[187,188] The dimensions of needles used for paediatric delivery may affect the amount of pain experienced and hence consideration should be given to the size of needle selected.[189] A survey investigating barriers to non-oral formulations in paediatrics reported a high rate (75 %) of barriers to parenteral formulations (IV, IM and SC). These included fear of pain and administration site effects such as bruising and bleeding, difficulty in correct use of the administration device and difficulty with preparation of dose.[190]

5.3.3 Long-acting technologies for the parenteral route

As stated in section 5.1.8, controlled/sustained drug release has several advantages. Recent technological developments for parenteral route dosage forms have focussed on prolonging drug release in order to improve patient compliance, and to simplify mass drug administration campaigns and logistics some examples of which are briefly described below. A key challenge for long-acting injections and depots for paediatric patients is the lack of flexibility in dose adjustment which is often required as a child grows. Furthermore, it is difficult to reverse the effects of the drugs administered, and neonates, infants and young children generally have less muscle mass than adults and depth of muscle and fat layers can vary.

FIGURE 11 Long-acting parenterals[191]



5.3.3.1 Nanosystems and Depots in Long-acting Injectables

Drug nanoparticles may be used as a means by which to increase the bioavailability of poorly soluble drugs by virtue of their large surface area which can enhance dissolution and absorption (see section 5.5.1). However, recent research has investigated the development and use of solid drug nanoparticles manufactured using emulsion-templated freeze drying (ETFD, University of Liverpool), for long acting injections for antiretroviral drugs (ARVs). Emulsion-templated freeze drying enables the manufacture of nanoparticles containing polymers and surfactants with very high drug loadings, for example over 70 %. This minimises the injection volumes required to administer the required doses. This process has also been applied to the manufacture of nanoparticles containing newly synthesised semi-solid ARV pro-drugs, which can also prolong drug release rate.[192,193] The University of Liverpool under the Unitaid-funded LONGEVITY project is using this method to develop fit-for-purpose products for malaria chemoprevention, TB prevention and hepatitis treatment for LMICs.[194] An example of a newly available long-acting injectable on the market formulated with nanotechnology is Cabenuva® (ViiV Healthcare), a once-monthly long-acting regimen consisting of rilpivirine and cabotegravir IM injections, that has recently been approved in Canada for the treatment of HIV-1 infection in adults.

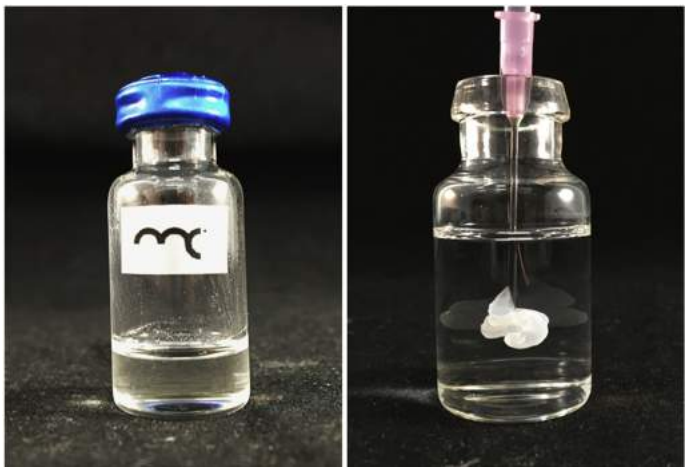
Long-acting (depot) injections have well established use in the areas of hormonal (progestin only) contraception and for the administration of anti-psychotic drugs and are designed to last for several weeks - months. They may be administered IM or SC, depending on the formulation. First generation anti-psychotic formulations were oil-based formulations for IM injection whilst more recent formulations are aqueous-based and can be injected SC or IM. Examples of formulation strategies to prolong drug release include the use of different drug salts, the development of crystalline suspensions, biodegradable polymeric microspheres and nanoparticles.[195,196,197,198] In contrast, nanosized-particles may be used for very poorly soluble drugs with long half-lives to provide depot injections with appropriate drug release properties.[199] Other strategies are proving important for allowing

more drugs to be combined in one formulation such as the Drug Combination Nanoparticle Platform (DcNP) employed by the University of Washington for developing products for HIV treatment, with support from NIH and Unitaid.[200]

In-situ forming systems have been investigated for long acting drug release. In these systems, drug formulations containing biodegradable polymer and water miscible solvent are injected SC after which they solidify ***in vivo*** to form an implant. Drug is slowly released via biodegradation of the polymer over a period of several months, however, the depot can be removed to terminate treatment. Hydrogels may be defined as 3D hydrophilic polymeric networks with a high affinity for water and other body fluids but are insoluble in them. Hydrogels can be modified such that they are sensitive to external stimuli including temperature, pH, magnetic field, light and glucose and injectable hydrogels have been developed that form sustained drug release depots after administration in response to for example body temperature. The rate of drug release from in-situ forming systems can be controlled by modifying the molecular weight and chemical composition of the polymers. It should be noted that any polymers used should be biodegradable, biocompatible and non-toxic. In-situ gelling injectable hydrogels have been studied extensively for targeted delivery of chemotherapy but may also be applicable for other indications such as diabetes and HIV.[201,202,203,204,205,206,207,208,209,210]

MedinCell BEPO® technology is an advanced in-situ forming depot. It uses a combination of two bioresorbable copolymers plus a solvent as excipients. It allows drug release to be adjusted from days to months. An additional benefit is the resulting products have a simple manufacturing process. Currently the technology is being developed for several purposes and notably for long-acting formulations for contraception and for vector control (ivermectin) geared to LMICs, with support from BMGF and Unitaid respectively.[211]

FIGURE 12 MedinCell BEPO® technology[212]

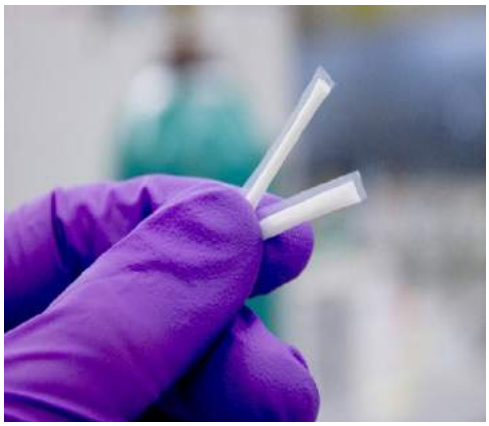


DelSiTech™ Silica[213] is a silica-based drug delivery system for controlled release, predominantly for parenteral products and local administration. It consists of a matrix of alkoxysilanes containing nanoscale pores with varying numbers of hydroxyl groups and water, into which small molecule drugs and vaccines may be embedded. The matrix can be designed to biodegrade at the required rate to ensure controlled release of the active substance over extended periods of time, via a process of erosion. In addition, the silica encapsulation process can provide stability to vaccines, allowing storage at room temperature.

5.3.3.2 Long-acting implants

Implants have historically been used for long acting hormonal contraception and are designed to last for several months - years. They comprise one or two flexible non-biodegradable rods (approximately 44 x 2 mm) which are inserted superficially beneath the skin and continuously release low amounts of progestin.[214] Implants may also be used for other indications where long acting therapy would be of benefit. Key advantages of implants include their convenience of use and the elimination of poor treatment adherence. However, they need to be inserted and removed by a trained healthcare professional. Two styles of implants have been described; matrix style whereby a drug is dispersed in a polymer which slowly biodegrades; and reservoir style which have a core containing the drug encased in a polymer membrane to control the release rate of the drug.[215] The safety and biocompatibility of all materials used in implants is of great importance. Other implant delivery systems under development include the Medici Drug Delivery System™ (Intarcia), which comprises a match-stick sized osmotic mini-pump with support from BMGF.[216] In addition, RTI International have been working on a long acting biodegradable implant for HIV prevention in women under the USAID Thin-film Polymer Device Injectable for Prevention Programme,[217] and a match-sized subdermal implant for sustained drug release is being developed by Oak Crest Institute of Science.[218] Further information on implants and and other long-acting technologies mentioned may be found in the Unitaid Long Acting Compendium.[219]

FIGURE 13 Long-acting implant.[220]



5.3.4 Needle-free injections

Needle-free injection devices have been developed to deliver drugs, hormones and vaccines subcutaneously, intramuscularly or intradermally. A fine stream of liquid or powder is forced under pressure through a narrow orifice and is able to penetrate the skin. The advantages of such devices include the elimination of the need for “sharps” disposal, reduced risk of needlestick injuries, a reduction in pain at the injection site and the ability of patients to self-administer. However, patients may still experience some discomfort, including a stinging sensation, and dose administered can be variable due to a lack of control of the jet parameters and differences in properties of the skin among individuals.[221,222] Needle-free injection devices are more costly than conventional hypodermic syringes and needles which may be a barrier to their adoption in LMICs, especially as alternatives are emerging. Examples of commercially available needle-free products and devices include InsuJet™,[223] ZOMA-Jet,[224] PharmaJet®[225] and Portal Instruments Drug Delivery Platform.[226]

5.4 Transdermal dosage forms

Transdermal drug delivery is a non-invasive alternative to the parenteral route providing therapy in a relatively painless manner which also avoid hepatic first pass metabolism. Common transdermal dosage forms include creams, ointments, gels and sprays which are predominantly used for local treatment, and transdermal patches which may be used for systemic delivery. However, a key challenge with transdermal drug delivery is the limited number of molecules that are able to pass through the barrier properties of the stratum corneum. Examples of commercially available transdermal technologies include Corplex™ (Corium),[227] Medspray® (MedPharm),[228] Micro-Patch self-injectors (Nemaura)[229] and TEPI Patch® (Medherant).[230]

Penetration enhancers can be used to improve transdermal absorption by interacting with the skin to create nanosized pores which improve permeability. However, their effectiveness can be limited and depends on the properties of the drug. In addition, the potential for skin irritation needs to be considered. Iontophoresis involves the application of a local electric current and can be used to drive hydrophilic molecules through the skin via the sweat glands and hair follicles. A disadvantage of this technique is the need for a device to generate and apply the required and appropriate current. Nanocarriers have been investigated for their application in combination with physical penetration enhancement techniques such as iontophoresis and ultrasound, to increase percutaneous penetration of drugs.[231] Recent research has shown that the topical use of drug encapsulated carbon (DECON) improved efficacy of the anti-viral acyclovir.[232] A new technology under development for the delivery of both large and small molecules via the skin is microneedles, which is discussed below.

5.4.1 Microneedles

Microneedles are either single or an array (patch) of multiple (up to several thousand) micron sized needles that can penetrate the epidermis and upper dermal layer of the skin but are sufficiently short to avoid stimulation of the pain receptors. They range from approximately 25 – 2000 µm in length, several 100 µm in diameter and 1-25 µm in tip thickness. Arrays of microneedles are attached to a backing such that it can be applied to the skin by hand, whilst single microneedles may be attached to a conventional syringe barrel. Microneedles have been investigated for cosmetic use, in diagnostics (e.g. for sampling small volumes of blood and interstitial fluids) and for the delivery of small and macromolecules including hormones and vaccines. Examples of the latter include vaccines for influenza, adenovirus, anthrax, hepatitis B, smallpox, malaria, measles, polio, rabies, HIV and West Nile virus.[233,234,235,236,237,238]

5.4.1.1 Advantages and disadvantages of Microneedle

Microneedles have shown the ability and potential to successfully deliver numerous small and large molecules. Unlike drug delivery via injection using hypodermic needles that is often painful and produces biohazardous waste (“sharps”), microneedles generally cause little if any pain, and can be easily disposed of. Furthermore, microneedles are easy to use and can be self-administered. An additional benefit is a simplified supply chain compared to conventional injectables since microneedles have a low bulk footprint and generally do not require cold (refrigerated) storage. The need for reconstitution before administration as required by many parenteral vaccines is also eliminated with microneedles, thus reducing cost and complexity. However, there are some disadvantages with microneedles. For example, mild skin irritation and erythema may occur with their application and there is a risk of infection caused by microneedle holes, although this is likely to be minimal. It may be costly and challenging to sterilise microneedles, especially since terminal sterilisation could damage them. It has also been reported that microneedles may have lower dose accuracy

and greater variation in drug delivery compared to parenteral injections depending on the condition of the skin. Since this is an emerging technology, pharmaceutical development guidelines for microneedles have yet to be defined although it is recognised that the safety and toxicity of microneedle materials, including their degradation products need to be evaluated. Further optimisation of microneedle manufacturing processes is required to ensure reproducible and accurate drug delivery at affordable cost.[239,240,241,242,243,244,245,246,247]

5.4.1.2 Acceptability of microneedles

Important attributes linked to the acceptability of microneedles include perceived or actual reduction in pain and ease and convenience of use. In contrast, barriers to microneedle acceptance may include unfamiliarity, potential for allergy and use of the word "needle" in name. The public and healthcare professionals are reported to have a positive perception of microneedles for use in children, especially for those who must inject frequently. In addition, positive responses from children regarding the use of microneedles as an alternative for blood sampling have been reported, as well as insulin delivery via microneedles being less painful than conventional administration methods. However, paediatricians have expressed concern regarding the potential for microneedles to cause skin irritation and consider them to be unsuitable for preterm neonates due to their immature skin. Interestingly over 75 % of healthcare professionals questioned expressed a preference for microneedles over conventional immunisation administration techniques. Furthermore, almost all adults participating in studies evaluating the acceptability of Intanza influenza vaccine given intradermally via a microneedle device (Soluvia®)[248] were satisfied or very satisfied and indicated a preference for being vaccinated by this method. In contrast, the microneedle device MicronJet® was not perceived to be better than a conventional syringe for multiple vaccinations at a single visit. It is suggested that this may be partly due to the appearance of the device since it comprises four microneedles attached to a standard syringe barrel.[249,250]

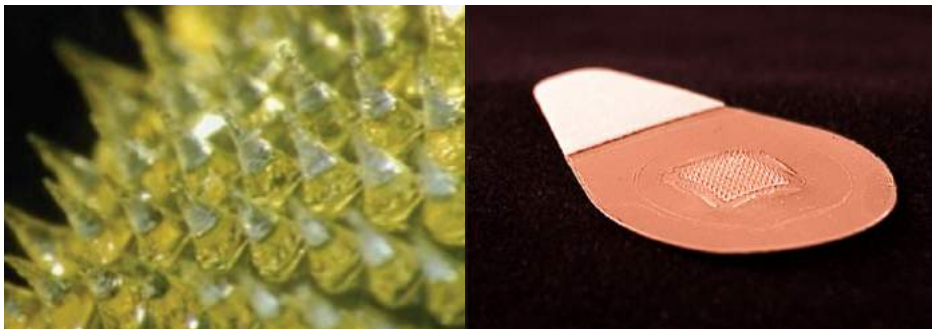
5.4.1.3 Examples of microneedle technologies

Microneedles can be classified into several different types, each with different mechanisms of drug delivery, as briefly described below. The materials used for their manufacture will depend on type of microneedle and properties of the drug, although all materials must be biocompatible. Commonly used materials include metals, ceramics, silicon, carbohydrates, sugars and both non-degradable and biodegradable polymers including hydrogels. Various techniques for microneedle manufacture have been investigated and developed including laser cutting, etching, micro-molding, lithography, 3D printing and droplet air born blowing.

Solid microneedles use the "poke and patch" approach for drug delivery whereby solid microneedles are applied to the skin to produce pores or micro-scale channels in the stratum corneum, after which they are removed, and a drug formulation subsequently applied (e.g. drug loaded patch). The drug permeates from the formulation through the microchannels via passive diffusion. Coated microneedles are solid microneedles coated with a water-soluble drug formulation and follow a "coat and poke" approach. On application, the drug is deposited in the skin and after the coated microneedles are removed, the drug dissolves and is absorbed. Since only low drug loadings are possible with coated microneedles, this approach is applicable for potent, low dose molecules, including vaccines. Hollow microneedles allow the flow of a drug solution or dispersion via active infusion or diffusion into the skin through the needle bores upon insertion, using a "poke and flow" approach. Hydrogel-forming microneedles start to swell upon application due to the uptake of interstitial fluid, and as a result of this they become a

rate-controlling membrane. Drug applied (via a patch) diffuses through the swollen microneedles into the skin. Dissolving and degradable microneedles are composed of drug incorporated within materials such as sugars and polymers which dissolve or degrade after insertion and upon contact with skin interstitial fluid to release the drug. This approach has been referred to as "poke and release". The rate of drug release can be controlled by modifying the swelling and/or degradation profiles of the polymers used. Unlike the other microneedle types, these microneedles do not need to be removed from the skin after application.[251,252,253,254,255,256,257,258,259,260,261,262,263,264]

FIGURE 14 Placebo microneedle patch[265]



Examples of commercially available microneedle technologies are provided in **Table 12**.

TABLE 12 Examples of commercially available microneedle technologies

Name	Company
Macroflux® (drug coated)	Zosano Pharma
MicronJet® (hollow)	NanoPass Technologies Ltd
AdminPen™ (hollow)	AdminMed nanoBioSciences LLC
DrugMat™ and VAXMat™ (dissolving)	TheraJect Inc
Microneedle patch technology (dissolving)	Micron Biomedical Inc
MicroCor® (dissolving)	Corium Inc
3M™ Hollow Microstructured Transdermal System (hollow) Solid Microneedle Technology (solid)	3M
Dermapen® (solid) (dermal/cosmetic use)	Dermapen
Dissolving microneedle patch (dermal/cosmetic use)	Nissha

5.4.1.4 Examples of marketed microneedle products

There appear to be very few currently marketed medicinal microneedle products, and several microneedle vaccine products seem to have been discontinued reasons unknown, for example Soluvia®.

Fluzone® Intradermal Quadrivalent (Sanofi) is an intradermal vaccine injection indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine (adults only). MicronJet®600 (NanoPass Technologies Ltd.) is a microneedle-based device for injecting fluids and is indicated for the intradermal injection of any substances or drug approved for delivery by this route.

5.5 Examples of supportive technologies

Examples of technologies that may be applied to more than one dosage form type and/or route of administration and which may have relevance for paediatric product development are discussed below.

5.5.1 Technologies for enhancing the bioavailability of poorly soluble drugs

Many drugs have poor aqueous solubility which can lead to limited absorption and poor bioavailability. Therefore, several strategies and technologies have been developed and employed to increase ***in vivo*** dissolution and absorption. By increasing the bioavailability of a drug, it may be possible to reduce the required dose, and therefore the unit dose size or volume of a formulation, which can be of benefit to paediatric patients.

Water-soluble organic solvents (e.g. glycerol, polyethylene glycol 400, propylene glycol) and /or surfactants (e.g. polysorbate, sorbitan monooleate) have been used to increase the solubility of drugs in oral liquid products.[266] Other approaches to increase drug dissolution include the use of different drug salts, alteration of pH complexation and increasing the surface area of drug particles by reducing particle size via for example micronization or nano-milling. As discussed in section 5.1.8, cyclodextrins are cyclic oligosaccharides which have a cone-like structure and are able to form inclusion complexes with other molecules, which can lead to an increase in drug solubility and bioavailability. Drug dissolution and bioavailability may be enhanced by the modification of drug crystal habit through the preparation of the amorphous form of the drug, and the preparation of co-crystals, solid dispersions and nanocrystals. In addition, various lipid formulations have been shown to increase the bioavailability of poorly soluble drugs. [267,268,269,270,271,272,273,274,275,276,277,278,279] Some of these technologies are discussed below.

Drug nanocrystals are nanoscopic crystals with a diameter of less than 1 µm whose use can lead to an increase in dissolution rate and bioavailability. Nanocrystals can be manufactured by a top-down approach whereby drug crystals are mechanically size reduced for example by milling, by a bottom-up approach whereby the nanocrystals are formed from a solution for example via recrystallisation or precipitation, or by using a combination of both. Nanocrystals are often formulated into nanosuspensions which are dispersions of very fine colloidal drug particles stabilised with surfactants in an aqueous vehicle. The average particle size of nanosuspensions is between 200 – 600 nm; particles less than 150 nm in size should not be administered since they may be internalised by cells via pinocytosis which can potentially cause cytotoxicity. Nanosuspensions have the advantage of being appropriate for delivery via various routes of administration including the oral, parenteral, ocular, rectal and topical routes and may potentially be formulated into liquid, semi-solid and solid dosage forms. However, they can be prone to chemical and physical instability for example agglomeration, sedimentation, Ostwald ripening and changes in the crystalline form of the drug.[280,281,282,283,284]

A key challenge to nanoparticle technology is the scale-up of the manufacturing process. Flash NanoPrecipitation is a new stabiliser directed raid precipitation process to produce nanoparticles. It uses engineered mixing geometrics to produce nanoparticles with controlled particle size anywhere between approximately 50 and 500 nm, with a narrow size distribution. Amphiphilic stabilisers and hydrophobic drugs are molecularly dissolved in an organic phase and mixed rapidly with an antisolvent stream to drive controlled precipitation. Since this is a continuous process, large batches of material may be produced by increasing the running time. Following precipitation, dried powder is obtained by spray drying, which may then be formulated into dosage forms.[285,286]

Other nanotechnologies are being investigated to enhance drug delivery. For example, drug-loaded mesoporous silica nanoparticles[287] and site-specific drug-loaded nano meshes comprising 200 nm diameter fibres produced using electrospinning.[288]

Solid dispersions are solids consisting of a hydrophobic drug dispersed in at least one hydrophilic carrier, (often polymeric), resulting in enhanced surface area and increased drug solubility and dissolution rate. The term amorphous solid dispersion (ASD) is used where the drug is embedded in the polymeric solid matrix in an amorphous form, which can have increased solubility compared to the crystalline form of the drug. Dissolution from solid dispersions is influenced by drug load, homogeneity, drug-polymer interactions and the presence of surfactants. It should also be noted that crystallisation of the drug can occur on storage potentially resulting in reduced solubility. Solid dispersions and ASDs are commonly manufactured by spray drying or thermal methods. As outlined in section 5.1.3.4, for the spray drying process, the drug is dissolved in a polymer matrix using organic solvents. The resulting liquid is pumped into a drying chamber through a nozzle where the fine droplets are dried to form particles, and the dry powder and wet gas are separated. Hot melt extrusion is a frequently used thermal process whereby solid materials are fed into an extruder barrel where they are mixed and heated causing them to melt. The melted soft materials are then forced through a die for further processing. During the process the drug is melted or solubilised in a polymeric carrier to form an amorphous dispersion. Solid dispersions and ASDs may be incorporated into dosage forms such as tablets and oro-dispersibles. Spray drying has the disadvantage of requiring organic solvents, whilst hot melt extrusion is not suitable to heat labile drugs. Kinetisol® technology is a process adapted from thermokinetic mixers and utilizes high shear to produce ASDs without extended periods of heating or the need for solvents.[289,290,291,292,293]

Lipid based formulations have been investigated for their ability to increase the bioavailability of poorly soluble drugs. The administration of lipids results in the secretion of bile salts, phospholipids and cholesterol which may enhance the solubility of any co-administered drugs in the GI tract and thereby increase absorption through acceleration of the drug dissolution process. In addition, lipid formulations may impact intestinal permeability, inhibit efflux transporters and facilitate drug transport via the lymph system. Examples of lipid formulations include oil solutions and suspensions, liposomes, emulsions (including micro-and nanoemulsions), self-micro- and self-nano-emulsifying drug delivery systems (SMEDDS and SNEDDS) and solid lipid nanoparticles. In addition, as described above, solid dispersions may be formulated using lipid-based carriers instead of polymers.

Liposomes are spherical phospholipid bilayer structures which are hydrophobic on inside and hydrophilic on outside. It is possible to embed drug inside vesicle or in the fatty layer. Liposomes can be used for oral, topical, transdermal and parenteral delivery. Niosomes are structurally similar to liposomes but manufactured from non-ionic surfactants rather than phospholipids. Self-emulsifying drug delivery systems (SEDDS) contain drug solubilised in an oily (lipid) vehicle mixed with surfactants, cosurfactants and cosolvents. They can emulsify spontaneously to form fine o/w emulsions in aqueous media with agitation. The size of the droplets formed determines the naming of the emulsion; SMEDDS (micro) contain droplets between 100 and 250 nm in size whilst the droplets in SNEDDS (nano) are less than 100 nm in size. Most SEDDS are liquids or semi-solid and are filled into gelatin capsules for administration. However, it is possible to prepare solid SEDDS by adsorbing them onto porous solid carriers such as silicon dioxide, calcium silicate or magnesium alumino-metasilicate, which can then be formulated into tablets or pellets/granules. It should be noted that extent of drug release from such carriers can vary and may depend

on the pore size of the silica carrier. Solid lipid nanoparticles (SLNs) are typically spherical particles 10 – 1000 nm in size with a solid lipid core stabilised by surfactants than can solubilise the drug thereby increasing bioavailability. Aqueous re-dispersible SDNs with high drug loading (> 50 %) have recently been manufactured by emulsion spray drying and are under evaluation. Lipid solid dispersions may be manufactured by spray congealing, whereby drug in a melted lipid carrier is sprayed into a cooling chamber maintained below the melting point, and on contact with air, the liquid congeals to form spherical particles. Lipid based granules or pellets may also be manufactured by melt granulation where a meltable lipidic binder is sprayed on or mixed at high shear rate with a powder blend.[294,295,296,297,298,299,300,301,302,303,304,305]

Milk contains between 3 and 6 % fat, 98 % of which comprises triglycerides. Hence the use of milk as a lipid-based formulation component for increasing the solubility and bioavailability of poorly soluble drugs has gained interest in recent years.[306,307,308,309,310,311]

Other technologies that may increase dissolution rate and bioavailability include the co-grinding of drug with pharmaceutical polymers or amorphous magnesium aluminosilicate. Mesoporous silica has very high surface area and pore volume which is thought to enhance the dissolution of drugs loaded on to these materials.[312,313,314,315,316] The application of electrospinning is being investigated for use in medicinal products, for example, oro-dispersible dosage forms (see section 5.1.5.4). The technology is based on the impact of a high electric field on drug-containing polymer solutions which generates polymer fibres in the submicron scale when the electric forces overcome the surface tension of the solution. For example, fibres with diameters between 100-300 nm have been produced. The fibres have a huge surface area which can lead to an increase the dissolution rate of poorly soluble drugs.[317]

5.5.2 3D Printing

3D printing (3DP) is an alternative manufacturing process for individualised dosage forms and may be defined as the production of a solid 3D object using a layer-by-layer process. 3DP is sometimes referred to as additive manufacturing and encompasses a range of different printing technologies. For example, fused deposition modelling involves the deposition of thin strands of melted polymer from a filament (often produced by hot melt extrusion), onto a build plate to form a layer. The process is repeated to build up the final object. During 3DP via pressure assisted microsyringe, a semi-solid formulation is extruded by pressurized air through a nozzle. Most formulations using this technique are solvent based and so a drying step in the process is required. In powder bed inkjet printing (binder jetting), a layer of powder is spread onto a plate followed by the addition of binder solution to bind the particles together and the process repeated, whilst in selective laser sintering, a laser is used to sinter the particles together instead of a binder solution. High resolution objects may be produced by this method although the potential for drug degradation due to the energy from the laser needs to be considered. Stereolithography is based on the solidification via polymerisation of a liquid resin by using a source of light. This method is also able to produce high resolution objects although a limited number of materials may be used.[318,319,320,321,322]

Since 3D objects are created from a pre-defined digital file which can be varied, numerous different dosage forms can be produced. Examples of 3DP dosage forms that may be suitable for paediatrics reported in the literature include mini tablets ("mini printlets"),[323,324,325,326] chewable tablets,[327] oral films,[328,329,330,331,332] oro-dispersibles,[333]

microneedle patches, suppositories and polymeric implants.[334,335] It is possible to modify drug release characteristics by using different polymers. In addition, 3DP can be used to produce bilayer or multi-compartment dosage forms (tablets) with more than one drug, each with a different release rate ("polypill"). [336,337,338,339] Thus, fixed dose combination products may be manufactured. As 3DP objects are produced by combining or depositing layers of material on a substrate, it may be possible to avoid drug incompatibilities by incorporating each drug in a separate layer.

A key advantage of 3DP is that personalised medicines tailored to the individual needs of the patient can be produced, potentially at the point of care (e.g.in a hospital or healthcare facility). Hence dose requirements can be easily met. It has also been found that commercial printers may be used although some modifications may be required. However, since this is an emerging technology for pharmaceuticals, regulatory requirements are evolving and may be unclear. Indeed, more focus appears to have been applied to the 3D manufacture and control of medical devices compared to drug products. In addition, the safety of any polymers used must be confirmed in the proposed patient population. For LMICs, the cost effectiveness of 3DP may be a challenge, especially due to the potential cost of production and intellectual property rights. A pharmaceutical 3D printer has recently been launched, M3DIMAKER™ for the manufacture of personalised medicines.[340]

The patient acceptability of 3DP dosage forms will very much depend on their characteristics. An exploratory study to investigate the influence of shape, size and colour on the acceptability (willingness to take, ability to swallow and opinions) of different placebo 3DP tablets in adults found that familiar shapes such as capsules and discs were acceptable, in addition to a novel torus shaped tablet.[341]

Currently only one 3DP drug product has been approved; Spritam® (levetiracetam) tablets for oral suspension.[342] This product is manufactured using proprietary ZipDose® Technology (Aprecia Pharmaceuticals).

6. KEY CONSIDERATIONS FOR APPLICATION OF INNOVATIVE DELIVERY SYSTEMS

As discussed in section 4, some the key challenges associated with the development and supply of paediatric medicines to LMICs include climatic conditions, fragmented supply chain, small market size, and cost.[343] A summary of key considerations for the dosage forms discussed above pertaining to their appropriateness for paediatric patients in LMICs and their potential application to LMICs is provided in **Table 13**.

TABLE 13 Summary of key considerations of potential paediatric dosage forms for limited-resource settings

Dosage Form	Age-appropriateness[1]	Limited-resource settings considerations
Oral routes		
Dispersible tablets (DTs)	From birth (reconstituted)	Undispersed DTs more stable and less bulky than liquids but may require moisture protective packaging. Limited dose flexibility although easy and simple to prepare and administer. No measuring required. Well established, non-complex development and manufacturing process with commonly available and relatively cheap excipients, unless novel/proprietary technology used. DT dimensions may be large for high dose drugs.
Mini tablets (1-3 mm)	Uncoated from birth, coated from 6 months	More stable and less bulky than liquids. Limited dose flexibility: commercial counting/ measuring devices are under development. Suitable for immediate and controlled release and may be taste masked. Can be administered as a direct dose or mixed with soft food. Well established, non-complex development and manufacturing process with commonly available and relatively cheap excipients. Limited drug loading per mini tablet and so multiple mini tablets required per dose for high dose drugs.
Multi-particulates (MPs) (granules, pellets, sprinkles)	From birth if mixed with liquid, or from weaning (approx. 6 months)	More stable and less bulky than liquids. Limited dose flexibility unless supplied with a measuring device. Can be immediate release, controlled release and/or taste masked. Can be administered directly or mixed with soft food/beverage and incorporated into other oral dosage forms (e.g. DTs, ODTs). Drug combinations may be achieved by mixing different drug-loaded MPs. Numerous manufacturing processes available; cost and drug loading will depend on method selected. Quantity of MPs per dose may be large for high dose drugs.
Oral films (oro-dispersible and buccal)	Oro-dispersible from birth Buccal – not known	Lower bulk footprint than liquids and portable but susceptible to high humidity and require moisture protective packaging. Limited dose flexibility although easy and convenient to administer with no mixing or preparation required. Can be used for modified release and drug combinations through multi-layered films. Requires specialized development and manufacturing facilities which may be costly. Limited drug loading and so unsuitable for high dose drugs. Buccal films avoid hepatic first pass metabolism and may be suitable for vaccine administration.
Oro-dispersible tablets (ODTs)	Depends on tablet dimensions; mini oro-dispersible tablets acceptable from birth	More stable and less bulky than liquids but may require moisture protective packaging. Limited dose flexibility although easy and convenient to administer with no mixing or preparation required. Direct compression method of manufacture relatively cheap. Other development and manufacturing processes e.g. lyophilization may be more complex and expensive but produce ODTs with quicker disintegration times. ODT dimensions may be large for high dose drugs.

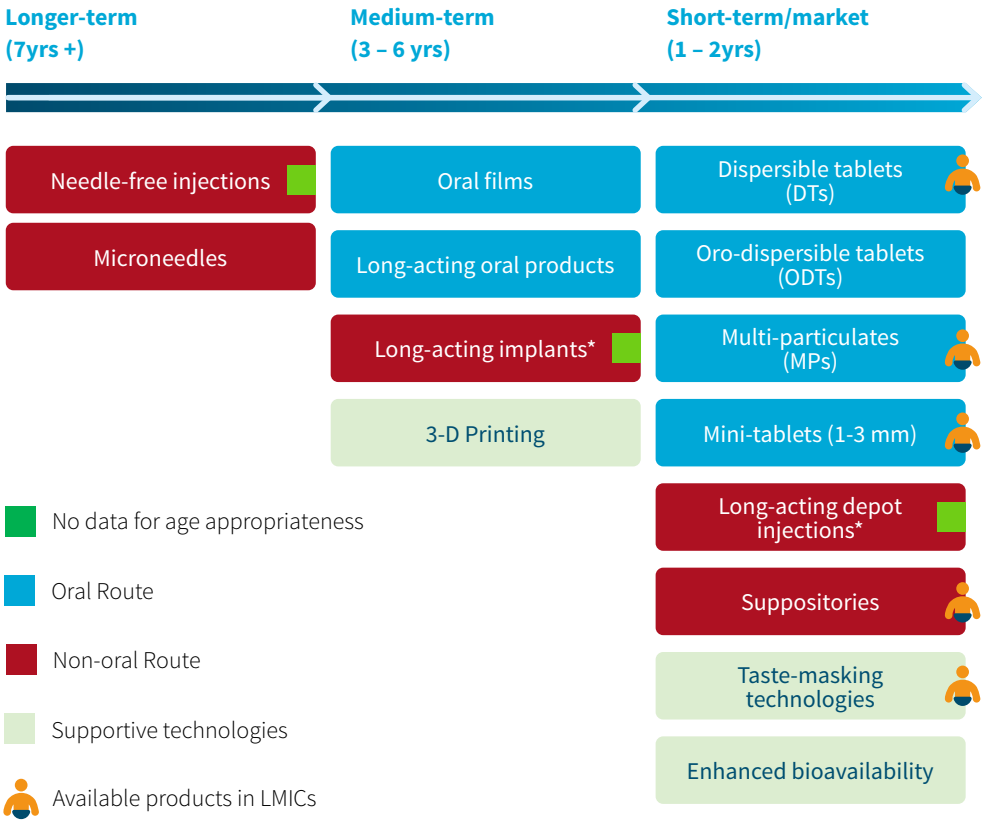
Dosage Form	Age-appropriateness[1]	Limited-resource settings considerations
Non-oral routes		
Long-acting (depot) injections (IM or SC)	No data	Liquid injection products are less stable and generally bulkier than solid dosage forms; lyophilised powder products have greater stability and are easier to transport but may be more expensive to develop and manufacture than liquids and require constitution before administration. Sterile products require specialised manufacturing facilities. Potential lack of dosing flexibility and may require a healthcare professional to perform administration. Risk of sharps injury and the need for safe sharps disposal and wastage management. May require large volume for high dose drugs. Infrequent administration required (weeks/ months) which can improve medication adherence, especially for long-term therapies, and simplify complex mass drug administration campaigns, reducing burden on healthcare professionals and care-givers.
Long-acting implants	No data	May have better stability compared to liquids and a lower bulk footprint. Development process can be complex and requires specialised manufacturing facilities. No dosing flexibility and may require large implant for high dose drugs. Requires a trained healthcare professional to insert and remove the implant. Infrequent administration required (months/years) which can improve medication adherence, especially for long term therapies, reducing burden on healthcare professionals and patients.
Microneedles	From birth	Potentially better stability than liquids (depending on microneedle material) and low bulk footprint. Low dose flexibility but are easy to use and can be self-administered or administered by caregiver. Dosing can be more precise if microneedles are embedded in patches (which can be made to size). Less painful than injections with needles, with no need for sharps disposal. Requires specialized development and manufacturing facilities which may be costly. Can be used for controlled drug release. May be unsuitable for high dose drugs due to limited drug loading but may be suitable for vaccine administration.
Needle-free injections	No data	Powder products have better stability compared to liquids. May require specialist development and manufacturing facilities and devices can be costly and bulkier than conventional parenteral products and administration devices. Can be self-administered and less painful than injections with needles, with no need for sharps disposal.
Suppositories	From 1 month	Can have limited stability in high humidity/ temperature and may require moisture protective packaging but have low bulk footprint compared to liquids. Limited dose flexibility. Can be self-administered or administered by caregiver. Provides a treatment route when children are unable to swallow oral formulations or when parenteral formulations are not available. Reasonably well established, non-complex development and manufacturing processes with commonly available and relatively cheap excipients. Can deliver high drug doses.

[1] Based on literature evidence for patient acceptability, where available

IV – intravenous; IM- intramuscular; SC – subcutaneous

With these considerations, the different delivery systems and approaches have been categorized by their availability or how close they are to being available to be taken to scale for any given condition. Those technologies that could be ready for "immediate" intervention and investment in the next couple of years are considered near-term. Whereas, those technologies that require more investment and R&D to mature are considered medium to longer-term opportunities for application into medicines required for paediatric patients in LMICs. This is illustrated in **Figure 12** and discussed in sections 6.1 and 6.2 respectively.

FIGURE 15. Potential opportunity for application of innovative delivery systems and supportive technologies for children in LMICs



**pipeline contains only application* for older ages

6.1 Near-term dosage form and technology opportunities

There are near-term opportunities for the development of age-appropriate solid oral dosage forms. Dispersible tablet (DT) formulations have been developed for diseases of interest in Low to Middle-Income Countries (LMIC) and continue to be a valuable platform for paediatric patients. Oro-dispersible tablets (ODTs) may offer a potential alternative and enable ease of dosing directly in the mouth without the need for product manipulation such as dispersion in water. The technologies commonly used for ODT development and manufacture are well established. However, the maximum dose of drug per ODT according to patient age may be limited by the need to ensure ODT dimensions are sufficiently small to minimise the risk of choking. Therefore, it may be necessary to utilise bioavailability-enhancing technologies to reduce dose size and ODT dimensions. Multi-particulates (MPs)

also offer near-term opportunities for paediatrics in LMICs: numerous MP technologies are available, many of which are well established. Method of manufacture can be selected based on the properties of the drug, required dose and release profile, and the ability to modify drug release and apply taste masking can be of benefit. Mini tablets can offer similar opportunities to MPs. However, since only a low drug loading may be achieved per mini tablet, it may be necessary to administer a large number for high dose drugs, which may lead to palatability issues. Hence, mini tablets may be more suitable for low-medium dose drugs.

Development of suppositories for LMICs has gained interest and is another potential near-term opportunity, especially with recent research into thermostable and prolonged release polymers for the rectal route. Another dosage form with near-term potential is long acting (depot) injectables, having well-established use, albeit mostly in adults. It should be noted, however, that such formulations may be less appropriate for neonates and infants, and their safety and efficacy in these patient groups needs to be confirmed.

Well established technologies for controlling and delaying release (for example, utilisation of polymers and lipids) and for enhancing the bioavailability of poorly soluble drugs (for example, through the preparation of the amorphous form, solid dispersions and nanocrystals, and application of lipidic excipients) are all considered to provide near-term opportunities. These technologies can be applied to many of the dosage forms described to optimise product performance, with a clear advantage on those such as patches that can enable administration by caregivers. Furthermore, conventional taste- masking technologies such as coating and complexation provide near-term opportunities.

6.2 Medium to long-term dosage form and technology opportunities

Further evaluation of the safety and acceptability of the following dosage forms and technologies in paediatric patients are required, as well as the feasibility for cost-effective commercialisation. Both oro-dispersible and buccal films may present medium term opportunities for paediatric patients in LMICs. They offer the advantages of being portable, have a low bulk footprint and are easy to administer, however, their limited stability in humid climates may be a challenge as well as low drug loading. For oral films to become more commercially viable for LMICs, their methods of manufacture need to become cheaper and the equipment required more readily available.

Progress is being made in the development of long acting implants. Although they can provide a huge benefit to patients on long-term therapies, there appears to be little research on their suitability for and safety in young children. Indeed, it may be possible to modify and reduce the size and drug loading of implants intended for adults. However, modification in the dose of drug released according to child growth is a key challenge and therefore long-acting implants may be more appropriate for adolescents than young children.

Although several needle-free injections are commercially available, their current cost and size may prohibit their application to LMICs, and alternative technologies may in the longer term be more appropriate. Microneedles have shown potential for the non-invasive delivery of drugs and vaccines and offer a valuable alternative to oral delivery, administration via needle injection and jet-injectors. However, the processes for manufacturing, testing and controlling microneedles need to be optimised before they can be clinically and commercially viable. Recent research into the development of delivery systems for the oral administration of dissolvable microneedles may in future provide an opportunity for

delivering vaccines and other biologic drugs orally. However, this work is currently at an early stage of development, and hence is likely its application to paediatrics is currently somewhat distant.

Various new technologies to prolong drug release may provide opportunities for drug delivery to paediatric patients. For example, injectable hydrogels, including those that solidify in-situ to form an implant, may offer a potential option for sustained drug delivery in paediatric patients. Indeed, the application of degradable hydrogel implants is likely to be less invasive than long acting sub-dermal implants. Gastro-retentive technologies show promise, especially for older children. The dimensions and physiology of the GI tract in paediatrics differs to that of adults and varies according to age and stage of development. Therefore, the safety and efficacy of gastro-retentive technologies need to be fully investigated in children.

Nanosystems also show the potential for medium-long term opportunities for paediatric development to enhance drug delivery. For example, solid drug nanoparticles with high drug loadings and silica-based systems. Flash NanoPrecipitation shows promise for the large-scale manufacture of nanoparticles, which can then be incorporated into various dosage forms.

The identification and utilisation of materials able to block the bitter aversive taste of drugs has the potential to greatly increase the palatability of paediatric formulations and enhance patient compliance. Although bitter blocker technology is likely to be drug specific, it offers significant benefits if applied to key drugs used for the treatment of major LMIC diseases.

Increased interest has emerged in the use of 3D printing for the manufacture of medicines, especially since the regulatory approval of a 3D printed drug product. 3D printing can produce personalised medicines according to the patient's needs, and hence this may have benefits for paediatric patients by ensuring their dose requirements are met. In addition, rate of drug release can be modified, and multiple drugs can be incorporated into one dose unit. Although this technology shows promise, manufacturing can be costly, and the safety of the polymers used in paediatrics needs to be evaluated.

In order to maximise potential opportunities, collaboration of different research groups should be encouraged so that expertise and promising technologies may be combined. In addition, input from all key stakeholder groups including academia, industry, clinicians, regulatory agencies and funders should be sought to optimise the development and supply of paediatric medicines in LMICs. There are groups collaborating towards these objectives such as GAP-f, European Paediatric Formulation Initiative, Goodman Pediatric Formulations Centre, among others.

7. CONCLUSION

Given the number of children that continue to die from preventable and treatable illnesses, there is an urgent need to reflect on life-saving medicines for which the delivery method could be improved so they can be effectively used in children of all ages and in all settings, as needed.

The breadth of technologies covered in this landscape analysis highlights the untapped potential to innovate and tackle the challenges in improving treatment and prevention of priority conditions affecting children in LMICs. With this awareness of the opportunities, stakeholders including involved in the research, development, and access of appropriate health products for children are encouraged to link these technologies to existing target product profiles (TPPs) and specific therapeutic compounds for which there are missing formulations for children.

The key question to ask in a review or matching exercise is "will an adequate formulation solve in a meaningful way a particular therapeutic issue for affected children?" Case in point, lopinavir/ritonavir which became available in 2003 was a life-saving combination, especially for the smallest children, for whom other therapeutic options widely used by adults for first-line HIV treatment were not available or appropriate. However, the youngest children living with HIV in LMICs, where the majority were born and die, could not adequately benefit from this medicine due to the lack of an optimal formulation for this age-group in LMICs. Through Unitaid's investment into a project led by DNDi, an adequate innovative formulation (4-in-1 granules containing ABC/3TC/LPV/r) was developed to result in expected launch price of less than US$1 a day.

Stakeholders involved with development of target product profiles and prioritization of paediatric formulations to be developed should be aware of the available delivery systems and formulation methods to be able to focus efforts on the best fit technology for a specific condition or medicine affecting children in LMICs that could have the most positive impact.

Certainly, key elements to ensure access for innovative technologies would need to be thoroughly planned as new products get developed, including measures to overcome potential barriers for market entry and country-adoption, for scalability and production capacity and for potential increased purchasing prices than current standards of care. There will be the need to demonstrate cost efficiency of improved formulations, and their expected public health impact in the disease burden and associated mortality.

Many of the delivery systems analysed in this landscape have the appropriate characteristics geared to access for LMICs related to temperature stability, potential for low cost production, and ability to manufacture at scale. Appropriate interventions and collaborations should be urgently put in place and existing initiatives should be leveraged (i.e., GAP-f) to prevent unacceptable delays in the application of these for the benefit of the most vulnerable populations: children in LMICs.

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