Innovative pharmaceutical techniques for Paediatric dosage forms: a systematic review on 3D printing, prilling/vibration and microfluidic platform

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HIGHLIGHTS

- The current pharmaceutical forms on the market, intended for the adult population, do not satisfy the needs of the paediatric population. For this reason, new technologies capable of meeting this market demand are to be investigated.
- 3D printing is functional to produce highly customised formulations for paediatric use due to its dimensional and dosage flexibility. Various 3D printing techniques investigated ensure the production of highly customisable pharmaceutical forms.
- The prilling/vibration technique guarantees the production of multiparticulates that are easy to swallow, flexible in the dose and can be administered in a user-friendly manner, making them suitable for the paediatric population.
- Microfluidics is an innovative technique that, due to its advantages, shows potential application to the production of micro-and nanocarriers for paediatric patients.

Innovative pharmaceutical techniques for Paediatric dosage forms: a systematic review on 3D printing, prilling/vibration and microfluidic platform

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ABSTRACT

The production of paediatric pharmaceutical forms represents a unique challenge within the pharmaceutical industry. The primary goal of these formulations is to ensure therapeutic efficacy, safety, and tolerability in paediatric patients, who have specific physiological needs and characteristics. In recent years, there has been a significant increase in attention towards this area, driven by the need to improve drug administration to children and ensure optimal and specific treatments. Technological innovation has played a crucial role in meeting these requirements, opening new frontiers in the design and production of paediatric pharmaceutical forms. In particular, three emerging technologies have garnered considerable interest and attention within the scientific and industrial community: 3D printing, prilling/vibration, and microfluidics. These technologies offer advanced approaches for the design, production, and customization of paediatric pharmaceutical forms, allowing for more precise dosage modulation, improved solubility, and greater drug acceptability. In this review, we delve into these cutting-edge technologies and their impact on the production of paediatric pharmaceutical forms. We analyse their potential, associated challenges, and recent developments, providing a comprehensive overview of the opportunities that these innovative methodologies offer to the pharmaceutical sector. We examine different pharmaceutical forms generated using these techniques, evaluating their advantages and disadvantages.

Keywords: Paediatric therapies, 3D printing, Microfluidics, Prilling, Age-appropriated therapy, printed tablets, nanoformulations, multiparticulates

1. INTRODUCTION

Paediatric patients have so far been considered “therapeutic orphans”[1] because pharmaceutical research and the development of innovative formulations have always focused primarily on adult targets[2]. For this reason, the practice of modifying through self-manipulation dosage forms designed for adult administration before being dispensed to children has become increasingly accepted[3], along with the off-label use of drugs (prescribed and/or administered outside the terms of their marketing authorization)[4]. These practices can easily result in the inefficacy of therapy or increased toxicity, thus representing a health hazard for the paediatric patient[5].

In addition, paediatric patients represent a very heterogeneous population, as the physiological characteristics of individual patients change very rapidly over time, especially in the first years of life. One product may not be suitable for all subpopulations, including preterm newborns, term newborns (aged 0–8 days), infants, and toddlers (aged 1 month–2 years), preschool children (aged 2–5 years), school children (aged 6–11 years), and adolescents (aged 12–16/18 years)[6]. The growth and maturation of a child, whether born full-term or prematurely, depend on intricate physiological, anatomical, developmental, and societal transformations. Recognizing the variations both between and within paediatric subgroups is essential for tackling the current difficulties and overcoming longstanding obstacles[7]. In summary, the paediatric patient population as a whole demands the greatest degree of dose adaptability. For this reason, there are numerous variables that must be considered during the development of a drug that is effective for the entire paediatric reference population (precise and appropriate dosage, swallowing difficulties, palatability and acceptability, excipient safety)[8]. Physiological characteristics of the patients affect the pharmacokinetics of the drug taken. Therefore, specific age-related formulations for children with precise dosing are required for effective and safe therapy[9,10].

For this reason, the European Union (EU) moved to find a solution to the existing gaps in the paediatric pharmaceutical market and in 2007 established the Paediatric Committee of the European Medicines Agency (PC-EMA), together with the mandatory Paediatric Investigation Plan (PIP). Thanks to these institutions, manufacturers could develop age-appropriate, safe, and effective formulations[11]. This should also facilitate the conduct of clinical studies in children, allowing for the marketing authorization of customized drugs in the paediatric population[12].

The current trend in the development of paediatric formulations is towards age-appropriate dosage forms, with considerations of acceptability, safety, and the ability to provide variable and accurate doses according to the child's needs. In addition, the dosage form must have acceptable palatability, contain appropriate excipients, and conform to regulatory requirements[13]. Conventional oral dosage forms for paediatric administration include both solid (tablets, capsules) and liquid (solutions, suspensions, and syrups) forms. Conventional formulations have limitations in the administration of drugs to pediatric patients since they were not specifically designed for this patient group. As a result, manipulation and compounding have become common practices[14].

Solid dosage forms were the pharmaceutical industry's favourite formulation due to their long-term stability, ease of supply chain, and lower production costs[15]. However, conventional tablets and capsules have some major disadvantages for the paediatric population. In fact, they have a non-modifiable dosage that forces patients to manipulate the medication, i.e. breaking the tablets. This practice does not allow the correct dose to be obtained, and there is also a risk of drastically altering the intended release properties of controlled or modified release dosage forms. The other main disadvantage comes from the inability of children to swallow such large dosage forms[16].

Liquid dosage forms have more limitations, such as problems with palatability, stability, difficult controlled release with the consequent need to administer multiple doses during the day and higher transport costs than solid dosage forms. Despite these limitations, liquid dosage forms may be favourable for some patients (e.g., infants and children) due to their greater dose flexibility and ease of swallowing compared to solid products[17].

Therefore, there is a need to develop new oral pharmaceutical forms specifically for paediatric patients that can meet their different needs and necessities.

Currently, the equipment and techniques used for industrial pharmaceutical production are not appropriate for creating small batches for age-appropriated therapy. This is due to the current commercial set-up, which makes the production of these small batches uneconomical for pharmaceutical companies, and therefore

unattractive[18,19]. As a result, several techniques have been developed in recent years to provide accurate and personalised dosages of active pharmaceutical ingredients (APIs). To realize the concept of age-appropriated paediatric therapy and individualized dosing of APIs, new technological approaches need to be considered[20]. The novel technologies that have emerged as the most useful approaches to the formulation of customizable pharmaceutical forms for paediatric therapy appear to be the pharmaceutical 3D printing, the prilling/vibration and the microfluidics techniques.

The aim of this review is to present the most significant innovations that these different techniques have introduced in the age-appropriated paediatric therapy field, leading to pharmaceutical forms that can be tailored to the needs of each child.

1.1. Paediatric Regulatory Legislation

With approximately 100 million people between the ages of 0 and 19, children account for over 20% of the population in Europe[21]. Despite this, more than 70% of commercially available drugs do not have paediatric authorization and have not been adequately tested or presented to the paediatric population, underlining how limited child-centred treatment is[17,21]. In order to overcome this severe limitation and thus ensure safer access to medicines for children, the European Paediatric Regulation (EC) N° 1901/2006 (Paediatric Regulation) entered into force on 26th January 2007[22].

A PIP is required by the Paediatric Regulation, which also created the European Medicines Agency-Paediatric Committee (EMA-PDCO) and mandated studies in the paediatric population, the results of which must be included in the marketing authorization (MA) documentation unless a waiver is granted. In order to postpone the release of some study results, it is also feasible to request a deferral. According to paragraphs 7 and 8 of the Paediatric Regulation, these rules apply to any novel or currently patented medicine for which an MA or an MA modification is requested. For the industry, incentives are available that include a 6-month extension of the supplemental protection certificate and an additional 2-year period of market exclusivity for paediatric orphan medical products (p-OMPs) to help offset the burden of this requirement[21].

In the years prior to Paediatric Regulation (2004-2006), the number of medicines (around 30) approved for paediatric use was very restricted. Ten years later, between 2014 and 2016, this number increased to 74 new drugs and indications. Although more new drugs and indications exist for paediatric use, the demand for paediatric-focused drug formulations is still high[17]. Meanwhile, there is a need to formulate paediatric pharmaceutical forms based on active ingredients currently developed for adult patients.

This demand could now be satisfied using innovative platforms that operate at the macro, micro, and nano levels of formulation. For each of these platforms, different technologies can be employed to obtain the finished pharmaceutical form. Among the numerous available techniques, we have investigated the most innovative ones such as pharmaceutical 3D printing for macro-formulation, prilling/vibration for micro-formulation and microfluidics for nano-formulation.

2. 3D PRINTING

In recent years, European regulatory authorities, primarily the European Medicines Agency (EMA), have focused their attention on the development of paediatric formulations, supporting the design of new strategies for their manufacturing[5] (**Table 1**). This marked the advancement of new therapeutic approaches, including mini-tablets (MT), chewable tablets and orodispersible films (ODFs), which, due to their high safety and efficacy, allowed the paradigm shift from liquid to solid dosage forms[23–25].

Table 1. Some examples of paediatric oral dosage forms on the market[26].

- **INSERT TABLE 1 –**

The utilization of three-dimensional printing (3DP) technology could represent an alternative approach for the pharmaceutical industry in the production of MT, chewable tablets, and ODFs. This innovative approach offers numerous advantages in terms of dosage form design and customization. In all these dosage forms, 3DP offers flexibility and customization, ensuring that medications are not only effective but also patient-friendly.

Also referred to as additive manufacturing (AM), 3DP is a technology that allows the creation of a finished object from a digital drawing by the sequential stratification of successive layers of material[27,28]. The information about the object to be printed is stored in a stereolithography file (.stl file), generated by computer-aided design (CAD) software. In order to achieve high variation and customized dosage, the digital file can be easily modified in real-time to adhere closely to the patient's needs[29]. Originally conceived only for the creation of new prototypes from newly designed products (rapid prototyping), 3DP has attracted considerable interest with consequent application in different and varied fields due to its versatility, ease of use, and low production costs[30,31]. Of particular relevance are the advantages of applying 3DP in the pharmaceutical field, as it is considered one of the most effective ways to develop patient-centred pharmaceutical products[32]. The high flexibility and easy adaptability of the production process make 3DP capable of customizing therapeutic strategies to respond to the physiological needs and unique lifestyles of each patient[33,34].

Hence, pharmaceutical research is currently focused on the possibilities of using 3DP to produce customisable dosage forms useful for adherence to age-appropriated medical therapies[19,35].

Thus, this enables the development and growth of precision medicine that involves optimizing drug doses according to the age, gender, weight, disease severity, and genetic profile of the patient[36]. In addition to customization, another important advantage of 3DP over the large-scale production achieved by traditional production systems is the realization of greater product complexity[32]. With this technology, it is possible to produce pharmaceutical products, denoted polypill, in which there is a combination of different active ingredients, taken daily by the patient, with specific release profiles and complex designs[18]. Printing in particular and diversified forms is particularly interesting for paediatric patients, who find concrete answers to their therapeutic and physiological needs in the use of 3DP in pharmaceuticals[37].

Several 3D printing techniques have been extensively explored for drug delivery applications and categorized into seven groups as per the 3D printing classification established by the American Society for Testing and Materials (ASTM), including Material Jetting, Binder Jetting, Sheet Lamination, Powder Bed Fusion, Vat Photopolymerisation, Directed Energy Deposition and Material Extrusion (**Fig. 1**)[38–41]. Out of these techniques, material extrusion stands out as the most frequently employed technique in pharmaceutical sciences, and in particular in the formulation of paediatric drug delivery systems (DDSs). The extrusion-based 3D printing technique has gained increased interest in the printing of pharmaceutical formulations due to its flexibility and the availability of pharmaceutical-grade materials[29,42] and the ease in accessibility of the involved printers[43]. This category encompasses three distinct techniques: Fused Deposition Modeling (FDM), Direct Powder Extrusion (DPE), and Pressure Assisted Microsyringe (PAM). Among these FDM technique, which involves the use of medicated thermoplastic filaments prepared through HME to achieve the final pharmaceutical form, represents one of the most extensively researched methods for developing pediatric DDSs[44,45]

Our review work focuses mainly on the treatment of extrusion techniques and in particular on DPE and PAM. Indeed, with these techniques, it is possible to obtain all types of solid or semi-solid pharmaceutical forms useful for age-appropriate medical therapy of paediatric patients. The development of polypills[46], immediate-release[47] and fast-dissolving[48] tablets, chewable tablets[44], and orodispersible films (ODFs)[49] for immediate drug release are some examples of how the 3DP PAM technique has been exploited to design pharmaceutical products in recent times. The DPE 3DP technique has been employed to develop immediate- and extended-release tablets[50], gastro-resistant extended-release tablets[51], and immediate-release orodispersible films[52].

- **INSERT FIGURE 1 -**

Fig. 1. Schematic representation of FDM (a), Direct ink writing (b), inkjet printing (c), stereolithography (d) and selective laser sintering (e) 3DP techniques. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [53].

2.1. Pressure Assisted Microsyringe

The semi-solid extrusion 3DP PAM technique was first used in the field of tissue engineering[54] and to date represents one of the most viable alternatives for drug printing in hospital settings for paediatric patients[49]. The use of 3DP PAM in pharmaceuticals offers the possibility to create complex dosage forms while avoiding the potentially difficult conditions sometimes associated with other printing techniques (e.g., FDM)[55]. Compared to DPE or other 3DP techniques that exploit solid starting material, the 3D PAM offers the possibility to print

formulations starting from liquid or semisolid materials. The printed formulation must have the ability to form a 3D object during printing without collapsing, so a focus must be placed on the source material used. The characteristics of the initial material enable the extrusion procedure to be conducted at reduced temperatures while maintaining both printing precision and the stability of the API. Furthermore, the use of pre-loaded, disposable cartridges simplifies the entire process[56]. Extrusion of the material through the syringe can take place by means of a pneumatic, mechanical, or solenoid system (**Fig. 2**)[57]. The use of these different material extrusion systems can lead to different characteristics possessed by the final pharmaceutical form, especially in terms of viscosity and accuracy of the form[58]. A second factor to consider when using this 3DP technique is the consolidation methodology used. In fact, if extrusion is carried out using high temperatures, the consolidation phase can take place by simple cooling of the extrudate. If, on the other hand, low temperatures were used in the extrusion phase, water or organic solvents must be used to obtain an extrudable blend, which will have to be consolidated through a drying phase of the pharmaceutical form to completely remove any residual solvent. An alternative is represented using photoinitiators that allow the polymers in the blend to photopolymerize and consolidate[18]. Initially used to produce polypills and tablets, this technology rapidly evolved to produce other types of dosage forms, from chewable tablets[44] to orodispersible films[49], to enhance paediatric patients' compliance with pharmaceutical treatment.

- **INSERT FIGURE 2 -**

Fig. 2. Schematic representation of 3DP PAM extrusion systems. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [59].

2.1.1. 3DP PAM Printed tablets

Solid formulations such as tablets are the most common oral dosage forms and the 3DP PAM could represent an interesting innovation in the field of tablet manufacturing. 3D-printed tablets can be developed with different release profiles (e.g., immediate or controlled release) to suit each patient's needs, or they can be produced to avoid swallowing (chewable tablets) so that they can also be administered to paediatric patients with dysphagia or swallowing difficulties.

2.1.1.1. Instant or controlled-release tablets

3DP PAM has proven to be a suitable technology to produce immediate-release tablets. An important advantage of 3DP to drug production is the possibility to customize treatments according to the needs of each patient. In a study by El Aita et al., immediate-release tablets of levetiracetam were prepared using the PAM technique[60]. Levetiracetam is used for epilepsy, where the dose in paediatric patients is increased over weeks. The aim of the work was precisely to prepare tablets that could be easily modified to follow the required dosage regimen. The tablets released the drug between 10-20 minutes, depending on the excipients used. In this way, it was demonstrated how this technique was able to customize the pharmaceutical form obtained in terms of dosage and drug release time[60]. Furthermore, in subsequent work, El Aita et al. produced levetiracetam tablets with a different number of layers to identify different doses for paediatric subgroups[61]. In this way, four different tablets with different numbers of layers were identified covering the dosage useful for therapy from infants (4 kg) up to preschool children (17 kg). The dissolution of the drug was dependent on the number of layers, and an increase in the number of layers resulted in a decrease in the drug release rate. All formulations disintegrated within 3 minutes, thus meeting the requirements of the European Pharmacopoeia (Ph. Eur.)[60].

2.1.1.2. Chewable tablets

Despite tablets being the most widely used and effective oral pharmaceutical form, about one in eleven patients experienced difficulty swallowing tablets and capsules[61]. Patients suffering from dysphagia have difficulties because the swallowing process is interrupted after ingesting solid or liquid drugs. Most of this percentage of patients is represented by the paediatric population. Often, to bypass tablet swallowing, medications are manipulated by crushing and dissolving them in water, greatly increasing the risk of therapeutic ineffectiveness

or overdose. Among the possibilities offered by 3DP PAM technology, the production of chewable drugs is one of the most applicable and relevant[44]. The production of easy-to-swallow formulations could greatly improve patient acceptability, especially in paediatric populations. A clinical study asked children between 4 and 11 years of age to choose the oral form of their treatment and 79% of them requested the chewable tablets[62]. Considering all of this, chewable formulations may represent a suitable alternative to enhance compliance in pediatric patients, as evidenced by numerous publications.

In children, taste, odour, and viscosity are also important characteristics that determine the acceptability of the formulation[63]. Goyanes et al. produced chewable cylindrical dosage forms carrying isoleucine. Isoleucine is used for the treatment of paediatric metabolic disorders, but its intake must be carefully dosed according to the patient's age, weight, and blood levels[64]. In the work, the printed formulations had different dyes and flavourings in order to identify which among them were most accepted by children (**Fig. 3A**). Most of the participants, who took part in this research, chose the orange-based formulations as their favourite[44]. Regarding doses, formulations were created with acceptable doses for paediatric patients, which rapidly released the amino acid within 5 minutes under simulated gastrointestinal conditions, showing less variability in the blood concentration of the drug compared to normal tablets[44].

Karavasili et al. made cereal-based dosage forms with varying concentrations of paracetamol and ibuprofen, hydrophilic and hydrophobic model drugs widely used as paediatric pain relievers. Also, in this case, the use of different designs and dyes led to greater acceptance by children. In addition, the use of cereals is important, as cereals are the most popular and well-accepted breakfast meal by children. The use of this expedient facilitated patients' intake of the drug by concealing it from the aspect of appearance and going to mask its taste, while simultaneously ensuring the absorption of the API[65].

Indeed, the use of foods to entice the paediatric patient to ingest the drug has been increasingly used, inspiring the use of chocolate as a vehicle for APIs delivery. Chocolate is important because it not only increases children's acceptance of dosage forms but also masks the bitter taste characteristic of many APIs. Chachlioutaki et al. and Karavasili et al. produced formulations based on bitter chocolate and corn syrup. Chachlioutaki et al. constructed cubic formulations in various sizes obtaining paracetamol carrier formulations with an acceptable dose for children (120-500 mg) with immediate drug release at pH 5.8[66]. Karavasili et al. chose to produce paracetamol and ibuprofen carrier formulations of various designs and sizes that could be liked by children, printed in different shapes reminding of cartoon characters (**Fig. 3B**)[67]. Concerning release, in simulated gastric fluids (pH: 2.0), the paracetamol formulation showed immediate release, while the ibuprofen formulation showed modified release[67]. Thus, in both works, a candy-like medicated formulation was obtained, easily assumed by the paediatric patient, while ensuring the proper dosage of the drug.

Finally, a variant of 3DP PAM involving extruding semi-solids within a solidifying liquid matrix has been used to produce chewable Lego™-like molds (**Fig. 3C**). Rycerz et al. produced formulations shaped like Lego bricks with different printing patterns and different colourations. The shape, size, and colour of the formulations made them more appealing to children[68]. Paracetamol and ibuprofen powders were suspended in a carob gum solution, forming a paste printed directly into a gelatin-based matrix. One of the advantages of this system is the ability to encapsulate the drug paste within a matrix that masks the taste, as in the case of some bitter-tasting drugs. The doses of paracetamol and ibuprofen for the obtained print patterns were appropriate for children[68].

- **INSERT FIGURE 3 -**

Fig. 3. Examples of chewable tablets with different shape and composition. Figure 2A is licensed under a Creative Commons CC-BY-NC-SA license adapted with permission from [44]. Figures 2B and 2C are licensed under a Creative Commons CC-BY 4.0 license with permission from [69].

2.1.2. 3DP PAM orodispersible films

Another interesting approach to improve drug acceptability by paediatric patients, in population groups with dysphagia, is the preparation of ODFs. The preparation of ODFs also allows the dose to be adjusted to the needs of each patient more quickly and directly by going to the extent and thickness of the produced films.

Paediatric ODFs containing levocetirizine hydrochloride, an H1 receptor agonist used to relieve symptoms of allergic rhinitis, have been produced using this approach[70]. In children, the dose of this drug depends on the

age of the patient and is commonly administered as an oral solution and fixed-dose tablets. Yan et al. exploited the PAM technique to achieve the printing of ODFs with a levocetirizine individualized dose for each age group, avoiding the need to divide commercial tablets and preventing dosing errors resulting from the use of oral solutions. The resulting ODFs, in fact, ensured instantaneous dissolution within the oral cavity and rapid absorption of the drug, thus presenting a viable alternative to the formulations available on the market[70].

Hence, the idea of producing ODFs using 3DP in the hospital setting as potential formulations to replace conventional compositions was explored with the preparation of warfarin loaded ODFs for paediatric patients, which include QR codes containing dosage form information[49]. Öblom et al. used the 3DP PAM technique to produce orodispersible films of warfarin sodium and compare them with conventional formulations consisting of oral powders in single-dose sachets obtained by crushing commercially available tablets. The films developed by Öblom et al. were characterized by large adhesion areas, capable of including a larger amount of drug if compared with conventional formulations, resulting more useful for paediatric custom therapies[49]. In addition, the flexibility of the obtained ODFs enabled administration through a nasogastric tube ~~possible~~, allowing a much larger number of hospitalized children to receive the therapy[49].

Therefore, the advantages of 3D printed ODFs include more accurate drug content than conventional formulations and easier conventional and easier administration directly into the patient's mouth without water. Apart from children or patients with swallowing difficulties, this approach could potentially be used to administer drugs to patients who are not adherent to treatment because ODFs are more difficult to intentionally expel from the mouth and do not cause choking during administration[52].

2.1.3. 3DP PAM related issues

The works cited above have demonstrated the ability of PAM to produce solid dosage forms. It should be kept in mind, however, that many processes involving the 3DP PAM technique are related to the use of organic solvents to achieve solubilization of excipients and API without incurring syringe and auger clogging[18]. The use of such organic solvents, such as acetone or DMSO, entails limitations in use for patients, particularly paediatric patients. According to the Ph. Eur., it is necessary to determine the residual solvent present within the finished pharmaceutical forms before production can proceed[11]. In addition, the preparation time of the formulations for printing the aforementioned study is quite long, taking 24 or more hours, making this technique unsuitable in the hospital emergency setting. These timelines are given not only by the set-up time of the printing stage, but also by the drying time of the pharmaceutical forms following printing[71]. To date, no study has analysed the printability of formulations over time. Since 3DP is inherently suitable for clinical applications due to its flexibility, the printability of a formulation after several days is of great importance. In order to reduce preparation time and drug waste (and thus the price per dose administered), larger quantities of a formulation are likely to be prepared and used over a period of time[54]. Therefore, further work needs to be done in this regard in order to administer a highly personalised product to the paediatric patient that is both safe and effective in every aspect.

2.2. Direct Powder Extrusion

DPE represents one of the most innovative 3DP techniques with the most promising applicability in the pharmaceutical field[29]. It enables the production of finished solid pharmaceutical forms in a single step, directly from mixtures of excipients and active pharmaceutical ingredients[43]. Therefore, DPE emerges as an evolution of other extrusion printing techniques previously employed, such as Fused Deposition Modelling (FDM)[72], which requires the use of filaments with specific physical and mechanical characteristics as raw material[73]. The removal of the filament production step, which precedes the printing step and is carried out by Hot Melt Extrusion (HME), extends the possibility of printing even mixtures excluded from FDM, especially those with high dosages of active ingredients, reduces the risk of degradation of active compounds exposed to double thermal stress, and accelerates the development of the formulation by lowering costs and production waste[29,74]. Thus, DPE offers clear advantages over the multistep FDM technique in terms of productivity, time efficiency, and selection of excipients and active ingredients, facilitating with one-step extrusion the production of customized pharmaceutical forms[74].

Also, from a technological-formulative perspective, DPE has an important advantage by allowing the formation of solid amorphous dispersions (ASD) directly during the printing process[29]. Indeed, ASD ~~is~~ used as a strategy to induce an increase in the water solubility of poorly soluble drugs, due to the high free energy acquired by the amorphous form of the drugs compared to their respective crystalline counterpart[75]. Consequently, this involves a higher dissolution rate of the drug and thus an improvement in oral bioavailability. In addition, the printing temperature is high enough to reduce the possibility of microbial contamination and the water content is very low, resulting in greater long-term stability of the drug[72].

2.2.1. DPE 3DP mini-tablets and orodispersible films

As previously stated, MTs and ODFs represent an innovative therapeutic approach that is gaining increasing interest in the field of macroformulation. In fact, Klingmann et al. demonstrated that the fear of choking that limited the use of common dosage forms in children can be overcome by the administration of MT, which is better tolerated and even safer than that of a common syrup in all children from six months onwards[23]. MT are not rigorously described by the normative guidelines and are associated with conventional tablets only presented in smaller sizes with a diameter of 4 mm or less[7]. In fact, just like conventional tablets, MT have a large spectrum of applications ranging from immediate drug release to prolonged, delayed, or pulsed release[5]. The first published study concerning the production of MT using the DPE technique was performed by Boniatti et al. in 2021[76]. The aim of this work was to produce a praziquantel (PZQ)-based formulation for paediatric patients that would not only address the market shortage of PZQ formulations suitable for children but also overcome the drug's main limitations, i.e., poor solubility in an aqueous environment and unacceptable taste. In particular, although PZQ has been the treatment of choice for over 40 years for schistosomiasis, a disease that alarmingly predominantly affects children aged 5-14 years, current paediatric therapy involves the off-label use of PZQ and dose adjustment through extemporaneous manipulation of tablets intended for adults, placing the paediatric patient at high risk of dosing errors and increased exposure to the drug's bitter taste. Therefore, Boniatti et al. proposed the use of the DPE printing technique both to obtain formulations with dose variability (100 and 150 mg) depending on the patient's weight and to make ASDs a solubility-enhancing and taste-masking strategy. Medicated physical blends, pellets obtained by HME, and powders obtained by milling the pellets all based on Kollidon® VA 64 and Kolliphor® SLS were used as feed materials for the printer. However, due to the poor flow properties of the physical blends and the absence of homogeneity in the particle morphology of the pellets, it was only possible to obtain printed tablets with high reproducibility from the extrusion of the milled materials. Solid-state characterizations conducted by DSC and XRPD had demonstrated the greater prevalence of the amorphous state of the drug as a result of the HME process and the DPE printing process, which was functional in inducing a more than fourfold increase in solubility compared to the pure drug as shown by dissolution studies. Furthermore, in vitro taste-masking studies had shown that the printed formulations released, even after 600 seconds, a drug concentration well below the thresholds classified as tolerable (0.05 mg/ml) and well-tolerated (0.03 mg/ml), demonstrating the potential of the DPE process in producing excellent amorphous systems for obtaining formulations designated with special attention to the paediatric patient[76].

The necessity of developing formulations with appropriate dose adjustments to meet the different needs of paediatric patients compared to adults was also addressed in the research work of Malebari et al[77]. Indeed, the authors focused on the study of a paediatric formulation against the human immunodeficiency virus (HIV), which, according to data collected up to 2018 by the World Health Organisation (WHO), affects more than 1.7 million children aged 0-14 years. Despite great progress in the treatment of HIV in adults, only half of the 52% of children with AIDS receive optimal therapy hindered by the unpalatability of the lopinavir (LOP) syrup boosted with ritonavir (RIT), Kaletra, recommended by WHO as a paediatric antiretroviral regimen. In the work, a detailed comparative analysis was made between FDM and DPE printing techniques to produce the same formulation, which clearly emphasised the advantages of DPE capable of maintaining a high drug content (above 90 %) while respecting the quality specifications guaranteed by the low extrusion temperature (80°C vs. 120°C for FDM), that did not lead to degradation of the active ingredients. DPE printing allowed the production of MTs with an acceptable size for swallowing, free of excipients recognized as not beneficial to children, such as propylene glycol and ethanol present in high quantities in Kaletra, and in which LOP and RIT were partially amorphized, resulting in an optimal dissolution profile. In fact, both actives have low oral bioavailability, associated with poor aqueous solubility at intestinal pH, which was however improved in MT dissolution studies in which drug concentrations were kept high even at basic pH. This represented an

important advantage in comparison to Kaletra, considering the increased fraction of the drug solubilized for prolonged periods and the variability of gastrointestinal pH in children.

In this regard, the realization of DPE MT coated with polymers sensitive to specific pH values was first proposed in the research work of Pistone et al[51]. In this study, the DPE printing process was combined with the fluid bed coating process to obtain budesonide (BD) loaded coated MT for the paediatric treatment of eosinophilic colitis (EC), a rare disease with a high incidence in the paediatric population. The absence, also in this case, of specific oral formulations for paediatric patients available on the market has found a possible positive response in the application of 3DP, and in particular in DPE, due to the high flexibility of dosage, the possibility of selecting appropriate shapes and sizes, which together allow the realization of a customized therapy. The authors focused on the study of different powder mixtures, which also included solubilizing polymers such as hydroxypropyl-beta-cyclodextrin (HP-β-CD) functional to enhance the aqueous solubility of BD through the formation of a ternary complex between the drug, the cyclodextrin, and the hydrophilic carrier polymer, such as hydroxymethylpropylcellulose (HPMC). Solid-state characterization studies carried out on printed MT using DSC, FT-IR, and XRPD revealed the acquisition of the drug's amorphous state, while release studies performed on uncoated MT allowed the identification of the formulation that would best result in an increase in aqueous solubility and dissolution rate of the drug, both of which were desired to ensure an improvement in the bioavailability of BD at the colonic level. Thus, the formulation indicated by the authors as MT2 underwent the process of coating with a pH-sensitive enteric polymer, Eudragit FS 30D, at different thicknesses, with the 6% coating proving to be the most effective in delaying drug release and making it possible only after exposure to the buffered solution at colonic pH (pH=7.4), as required for EC treatment.

A first study on the application of 3DP DPE for the production of oral mucoadhesive films was conducted by Racaniello et.al[52] in response to an unmet medical need for a customized treatment for paediatric patients affected by Oral Lichen Planus (OLP), a chronic mucocutaneous disorder that predominantly affects the oral mucosa. The drug selected was clobetasol propionate (CBS), commonly used for the treatment of this pathology, in a dosage of 125 µg/dose, therapeutically appropriate for the paediatric patient. To guarantee a rapid dissolution of the formulation in the oral cavity, hydrophilic polymers were used, such as HPMC, polyethylene oxide (PEO), and chitosan (CS), widely used in the pharmaceutical field for their mucoadhesive properties due to establishing interactions with the mucins of the mucosa. In addition, HP-β-CD was also used in this study to improve the aqueous solubility and dissolution rate characteristics of the drug. Of the four powder blends initially investigated and characterized by different ratios of PEO to CS, only those indicated by the authors as Blend2 and Blend3 proved to be excellent feedstocks for the DPE printer, allowing films with an elastic and tenacious structure to be obtained. The good mucoadhesive properties of the printed films improved with increasing CS concentration within them, which however was verified to have a negative influence on CSB retention in the epidermis. Despite this, the obtained films presented insignificant permeation of the drug from the epithelium and considerable resistance to the scavenging phenomenon, seeking to enhance and prolong the action of the drug locally.

2.3. 3DP industrial scalability and related issues

The 2015 market launch of Spritam® by Aprecia Pharmaceuticals following FDA approval of the product and production methods has already demonstrated the industrial scalability of the 3D printed dosage forms and the 3D printing technique, showing how the production and distribution of a 3D-printed drug is possible while maintaining control over quality and production costs. However, the industrial scalability of 3DP in the pharmaceutical industry to date represents a challenge involving several factors. One of the main obstacles consists of optimizing production speed and productivity, as current processes can be time-consuming. Technological advancements should aim to address the need for scalable and cost-effective printing systems[78]. It must be considered that this kind of technology is designed for the production of smaller batches, tailored to a small number of patients, and is therefore not directly comparable with the means currently available to pharmaceutical companies to meet the demands of the normal market[79]. Furthermore, it is necessary to identify and qualify production materials and excipients used that meet regulatory standards and possess the necessary mechanical and chemical properties for pharmaceutical applications. Regulatory standardization is essential, requiring the development of robust standards and protocols for 3D printed pharmaceutical products[80,81]. Critical quality attributes (CQAs) are essential for 3D-printed solid oral dosage forms to ensure efficacy and dependability. One crucial characteristic is layer deposition precision, which directly impacts dosage uniformity and accuracy. The mechanical strength and integrity of the printed structure are also

essential components to guarantee the tablets and oral films effectiveness during handling, transportation, and storage[82]. Surface smoothness is a further critical variable that can affect the overall bioavailability and dissolution rate of the drug. To achieve optimal drug release characteristics, it is crucial to tightly regulate the porosity and density of the printed structure[83]. Meticulous monitoring during the process and post-production testing for quality control and assurance are required to ensure the continued safety and efficacy of large-scale printed pharmaceutical products. Attention must be paid to the stability of the formulations obtained and biocompatibility to ensure patient safety and health, especially in paediatric therapies[81]. For this purpose, it is necessary to establish the degree of cleanliness and process validation, which are currently still lacking for all 3D printing techniques[45]. In this regard, important development steps are already being taken, focusing mainly on the most widely used 3D printing techniques in the pharmaceutical industry, such as FDM. In fact, entities such as the PolyPrint consortium are currently engaged in the creation of innovative polymers for 3D printing with FDM, the formulation and production of filaments, process optimisation and the design of a GMP-compliant FDM printer[84]. The successful integration of large-scale 3DP in pharmaceutical production will depend on achieving a balance between customization and standardization, managing costs, and promoting continuous technological innovation. Indeed, it is possible to identify useful models for pursuing this aim in a hypothetical massive distribution of 3D printing technology in the pharmaceutical market. Standardisation of processes and material specifications would primarily reduce the development time of compounds to be extruded, ensuring uniformity and consistent quality in the final results[85]. This could include specific printing protocols, selection of approved materials, and specific quality control procedures for each active ingredient and dosage form. By standardising printing methods, it would also be possible to create a network of geographically distributed production centers, each certified to meet quality and safety standards. These centers could be centrally regulated to ensure standards and regulatory compliance, through a single quality control system that monitors material quality, temperature, printing speed, and other critical variables, allowing timely intervention to prevent defects or anomalies. The process of standardising procedures and materials would also favour the automation of production processes, minimising errors and reducing downtime in the production process and overall production costs[79]. Finally, from a financial point of view, flexible business models could be introduced such as differentiated tariffs according to the complexity of the customised treatment required, customised service packages, and subscription models to ensure constant revenue for the company. These solutions could potentially lead to the successful industrial scalability of 3D printing as a form of customised drug batch production.

3. PRILLING/VIBRATION TECHNIQUE

Multiparticulates/granules (MPs), unlike classic single-unit dosage forms such as tablets, include a multitude of spherical particles with a diameter of 0.1-2.5 mm combined in a single dosage unit and can be pellets, granules, or microparticles (microspheres or microcapsules). MPs offer many advantages over traditional single-unit dosage forms; they ensure greater and more uniform distribution in the gastrointestinal tract with less risk of irritation and toxicity, increase bioavailability and reduce the incidence of local irritation and toxicity[86]. MPs are versatile dosage forms as they allow formulations to be developed with the required release profile (modified, prolonged, delayed, etc.), optimising pharmacokinetic profiles and reducing the frequency of administration[87]. This can be achieved by simply combining MPs with different APIs and/or different release characteristics into the same dosage form, respectively.

Microparticles offer advantages in formulating multi-particulate and multi-unit pharmaceutical dosage forms. This improves drug safety and efficacy, with favourable pharmacokinetics. Patient safety is the primary focus, with improved ease of administration, increased compliance, and a better overall patient experience. Microencapsulation is one of the most effective methods to produce particles for controlled drug delivery systems[88]. Among the various physical methods for microencapsulation, such as the well-known spray drying, spray congealing, electrospinning, emulsion process, fluidised bed coating, and extrusion, the microfluidics, and the prilling/vibration technique, have received significant interest mainly due to their simple approach to producing homogeneous microspheres and microcapsules with the desired characteristics[89,90] (**Fig. 4**). ~~Indeed,~~ This section focuses on prilling/vibration, a versatile and precise pharmaceutical manufacturing technique, has gained recognition as an ideal method for formulating paediatric dosage forms such as MPs[91]. It has recently emerged as a promising technology to produce microparticles with a narrow particle size distribution, high encapsulation efficiency, great versatility, reproducibility, and high scalability potential[92].

- **INSERT FIGURE 4 -**

Fig. 4. Graphical schematisation of the most commonly used techniques for obtaining MPs. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [93–97]

Several advantages are associated with this technology and its use in the pharmaceutical sector. The vibrating-jet technique, more commonly known as the vibrating nozzle technique or Prilling/vibration is a promising technique for the continuous production of large quantities of uniform spherical microparticles, both microspheres and microcapsules which fall into the class of MPs, with excellent flow properties that can be successfully inserted into capsules or sachets[98]. The prilling/vibration technique is based on breaking a laminar flow of a polymer solution pumped through a syringe into a nozzle. This is achieved by applying a vibrational frequency, resulting in the formation of one-dimensional droplets, or prills. The resulting droplets fall into a gelling polymer solution in which they solidify as microparticles.

In detail, as can be seen from **Fig. 5**, the polymeric feed solution is pressurized using a pump or gas through a nozzle to generate the liquid jet. The viscosity of the polymer feed is certainly one of the most important variables in this technique. A laminar flow liquid jet is produced when a polymer liquid (containing the material to be encapsulated) is extruded through a selected nozzle. Either a monocentric (single-flow) nozzle can be used to produce microspheres, or a concentric (dual-flow) nozzle can be used to produce microcapsules. In the first case, the polymer feed contains the material to be microencapsulated. In the second case, there are two different polymer feeds, one forming the core where the encapsulated material will be present, and the other forming the shell, i.e. the coating material.

A laminar jet of liquid extruded through a nozzle can spontaneously fragment into droplets of varying size due to natural perturbations, with no possibility of complete control. However, according to Rayleigh's theory, a controlled break-up of the jet into uniform droplets can be achieved by applying a sinusoidal force at specific frequencies. When a liquid is pushed through an orifice by applying a low flow, droplets of equal size are formed; if a mechanical vibration is applied to this dripping mechanism along the flow axis, the flow breaks up and the droplet size is reduced in a controlled manner[99]. Hence, as the polymer feed is extruded through a chosen nozzle, generating a laminar flow liquid jet, a controlled, superimposed vibrational frequency at a defined amplitude is applied to this jet. This action causes the jet to break up into small, uniformly sized droplets, with one droplet formed per hertz of the applied frequency. To prevent the coalescence of the droplets during jet break-up, an electrical charge is induced on the surface of the droplets using an electrostatic voltage system placed directly below the nozzle. The charged droplets are deflected from their vertical position so that the impact occurs over a larger area in the curing solution. At this point, the spherical droplets fall into the gelling bath and consolidate to produce mono-dispersed MPs[100].

- **INSERT FIGURE 5 -**

Fig. 5. Schematic representation of the microencapsulation process.

For microparticles to form, polymer droplets must be able to solidify, and solidification processes occur through various methods, including temperature, chemical cross-linking, pH, and non-solvent-induced phase separation. Temperature-induced gelling, also known as thermotropic gelling, occurs when polysaccharide molecules associate in an oriented form in response to temperature. This phenomenon is observed in agarose, carrageenan, and starch. On the other hand, pH-induced gelation occurs by altering the pH of the solvent. Polysaccharides dissolved under alkaline or acidic conditions can undergo gelation by changing the pH of the solvent medium. Gelling occurs at the point of contact between the acid or alkaline solution and a droplet of polysaccharide solution, forming a shell. Complete gelation is then promoted by the diffusion of ions through the shell. To ensure complete ion diffusion and consolidation of the polymer feed, a high concentration of acid or alkaline is typically maintained in the regeneration bath. This method is primarily used to prepare gel particles of chitosan, pectin, and alginic acid. Non-solvent-induced phase separation is a method for producing particles through a coagulation process that is not induced by solvents. The process involves adding a non-solvent to a polysaccharide solution, causing the polymer to separate into polymer-rich and polymer-poor regions due to a decrease in solubility as the proportion of non-solvent increases. This separation is initiated by the diffusion of the polymer solution. Ionotropic gelation is a process that occurs when a solution of alginate or pectin meets a solution containing divalent cations, usually calcium. This process follows the 'egg-box' model, in which calcium ions bind to four carboxyl groups belonging to different alginate chains. The gelling of

pectin is induced by calcium, depends on the degree of esterification and is more pronounced when using pectin with lower degrees of methylation and at a pH of about 3-3.5. Chitosan, which contains an amine functional group, can undergo ionotropic gelation when exposed to anionic counter ions such as tripolyphosphate, sulphate, and citrate. This process entails the creation of electrostatic interactions between the cationic chitosan and the anionic counter ions, which facilitates the formation of a gel network. The properties of the resulting particles are influenced by the polysaccharide source, composition, concentration, and processing conditions on which these gelling processes depend[101].

In the prilling/vibration technique, many factors influence the formation of microparticles ~~microgels:~~ such as the concentration, feeding rate, and surface tension of the polymer solution, solvent, temperature, and nozzle diameter. These factors are important and decisive for the characteristics of the microparticle results, i.e. the particle size and the physical properties of the MPs (gel strength, porosity, etc.) [102]. The aim is to produce small droplets/microcapsules with low size dispersion (less than 10%) with a good level of output[103]. The size of the produced droplets and the rate of production are mainly dependent on the nozzle size, the flow rate and viscosity of the extruded liquid, and the vibrational frequency applied. These parameters can all be controlled. For example, it is possible to change the nozzle used, i.e., the nozzle size (µm), which influences the size of the MPs that will be produced. It is important to set the flow rate or flow rate (mL/min), i.e., the speed at which droplets are formed, and the vibration frequency of the membrane, which determines the number of droplets and microparticles that are formed.

The CQAs of microspheres produced by the prilling/vibration technique are of great importance in determining their efficacy and applicability in various applications. It is essential to consider the size, shape, and homogeneity of the microspheres as key parameters to ensure reproducible results and consistent performance. It is also important to assess the porosity of the microspheres as this can affect the loading capacity of the active ingredients. The thermal and chemical stability of the microspheres must also be considered to ensure their durability and integrity during production, storage, and use. MPs have been studied for their increased safety compared to single-dose modified release systems, which could result in a massive dose release if the modified release technology fails after administration. In the case of MPs, each subunit of the delivery system is coated with polymer individually. This reduces the likelihood of massive release, as the failure of only a few subunits would result in the release of only a small fraction of the intended dose. This ensures the effectiveness of the designed release profile.

The Prilling/vibration technique is an advantageous innovative encapsulation technique, is simple, extremely efficient, low cost, and capable of being scalable, with the possibility of producing formulations with high encapsulation efficiencies, yields and used to obtain microparticles with a narrow size range. Particle production via the vibrating nozzle device is easy to scale out, e.g., by using a multi-nozzle system without changing other process parameters such as flow rate and vibration frequency[104,105].

Compared to other techniques used to produce MPs, such as spheronisation, granulation, and fluid bed that need to continually expose the microencapsulated material to high or low temperatures or humidity, which is a problem for temperature-sensitive materials (e.g., thermolabile APIs, probiotics, enzymes) and oxidation-prone molecules (e.g., vitamins), the prilling/vibration technique can operate under mild conditions. It does not require particularly high temperatures, and above all, it uses aqueous solvents and does not require organic solvents.

This technique ensures the use of a wide class of both natural and synthetic polymers suitable and approved for paediatric treatments. The natural raw materials have good biodegradability, and their decomposition products are safe and non-toxic to the body. They include polysaccharides (alginate, chitosan, cellulose and its derivatives or agarose) and proteins (fibrin, gelatine, collagen, and bovine serum albumin) while the synthetic polymers are, for example, PLGA, PLA, and different types of polyesters and polymethacrylates. The use of a wide range of polymeric excipients allows the formulations produced to release the microencapsulated active ingredient in a modified manner both in time and space (targeted release system) to optimise the drug's effect[106]. This technique allows microparticles with different APIs, which would normally not be compatible, to be produced and then co-administered in a dose form. The presence of several small MPs reduces the likelihood of adverse effects and minimises the chance of a dose-dumping effect. The small size of the subunits, compared to a single unit modified-release dosage form, reduces dependence on stomach emptying rate, resulting in minimal intra- and inter-personal variability in gastrointestinal transit time. MPs ensure a reduction in side effects, improve the stability of the active ingredient in the formulation and protect active ingredients susceptible to oxidative processes[107].

Despite the many advantages of this technique, there are some limitations to be considered, which represent a challenge for researchers to overcome. For example, the use of an aqueous consolidation bath could result in a partial loss of the microencapsulated material, with reduced encapsulation efficiency values, which may escape from the not fully formed network of the polymer matrix that is still present in a transient semi-solid state[108]. This, however, depends on the characteristics of the polymer feed used and the encapsulated material especially its solubility and its ability to diffuse in the aqueous bath rather than being trapped in the polymer network, which becomes increasingly dense during the consolidation process. The generation of particles in aqueous dispersion may pose drawbacks, especially when a subsequent drying method is not advisable. Furthermore, specific essential criteria, such as maintaining a consistent solution drop rate and ensuring controlled agitation, must be considered. It should be noted, however, that in addition to aqueous crosslinking baths, where this problem is easily solved by a careful initial study of the process variables, there are other crosslinking methods such as liquid nitrogen. In this case, the polymer feed falls into liquid nitrogen and freezes immediately, avoiding the losses that can occur in an aqueous bath due to diffusion processes during the crosslinking process.

One possible drawback of this technique is the restricted scope of research which includes only a few studies. Nevertheless, this constraint can be transformed into a prospect by investigating fresh alternatives and persisting in the ongoing exploration to advance the technique.

3.1. Multiparticulates in paediatric therapies

MPs offer distinct advantages in the formulation of paediatric pharmaceuticals, making them a preferred choice for dosage forms tailored to children's needs. Their smaller size and uniformity allow for precise control over drug content, enabling accurate dosing for paediatric patients, whose medication requirements often vary based on age and weight. MPs are especially useful in creating oral suspensions and dispersible dosage forms, where they can be easily reconstituted in liquids, ensuring ease of administration, particularly for young children who may have difficulty swallowing solid tablets. Furthermore, MPs offer the potential for taste masking and flavouring, addressing one of the key challenges in paediatric medicine, as ensuring palatability can significantly enhance medication adherence. Overall, the attributes of MPs, including their size, uniformity, and versatility, make them an excellent choice for the development of paediatric pharmaceuticals, optimizing both efficacy and patient acceptability. MPs are versatile dosage forms that provide a desired release profile. The development of modified-release formulations is encouraged for paediatric patients, as suggested by the EMA guideline regimen[109]. These formulations can significantly reduce the frequency of administration, making them useful for children who would otherwise have to take the drugs while at school or overnight. When developing modified-release oral drug formulations for paediatric use, it is essential to pay particular attention to the physiological conditions related to the child's age, e.g. gastric pH and gastrointestinal motility (gastric emptying, transit time) and their variability, as these characteristics may have a significant impact on the drug release profile and absorption.

MPs are considered to combine the advantages of both liquid and solid oral products as they are characterized by enhanced swallowability and flexibility in dosage while having stability characteristics and low microbiological risk comparable to those of classic tablets[110]. Since each unit contains a small amount of the drug, the recommended dose can be prepared with a dosing device or by measuring a specific weight/volume. For this reason, MPs represent a flexible and precise dosage form that can be administered safely and completely, meeting the dosing needs of all age groups, unlike conventional formulations that are not always appropriate for paediatric patients and require dose manipulation while compromising the drug's release characteristics influencing both safety and efficacy[14]. Flexibility and dosage versatility are the two main advantages that make MPs suitable for paediatric pharmaceutical forms. Individual particles can be sprinkled on meals for younger children or formulated as chewable tablets or ODTs for older children and adolescents. Additionally, a high drug load can be achieved, which is advantageous compared to the use of large tablets or capsules. It is believed that administration with MPs is easier than with single-unit formulations because more pellets are used to produce the required dose, which avoids the potential variability often associated with dividing single-unit formulations. This high dose flexibility can be achieved by measuring a specific weight or volume of sub-units based on body weight or body surface area when dose adjustments are required[111].

A key challenge in the development of pharmaceutical forms administered orally to paediatric patients is the acceptability, palatability (taste, aroma, texture, and mouthfeel), appearance, colour, size, dosage frequency, dose flexibility and organoleptic properties of the final pharmaceutical form[112]. MPs are easy to swallow and are acceptable for children after weaning (from about six months) although they may also be suitable for toddlers and infants if administered in a liquid vehicle[113]. Acceptability parameters for MPs to consider include taste, particle size, ease of administration, volume, and consistency of the particles in the mouth[114]. Although the acceptability of MPs in terms of grittiness or texture in the mouth is not completely known[115], there is evidence that the quantity, i.e., the dose of MP, is the most significant factor in determining the perception of grittiness.

The choice of the delivery device is an important factor in the general quality and acceptability of the drug. Commercial MPs drugs are typically in the form of pre-filled unit-dose capsules or sachets where the appropriate dose is pre-packaged[116]. MPs can be sprinkled into suitable baby food or swallowed directly by using a dose-measuring device, e.g., a measuring spoon or dose-sipping technology (**Fig. 6**). It consists of a straw containing the microparticulate that is ingested in combination with a liquid of choice present in a glass. In this way, the young patient can scarcely taste the MPs, increasing acceptability and adherence to treatment[8]. Although the small size of MPs (350-750 μm) does not significantly affect swallowability, one study found that increasing the particle volume fraction by more than 10% reduced the percentage of swallowed particles[117]. However, MPs were still easier to swallow than minitablets. To ensure that the microspheres produced using the prilling/vibration technique meet the required standards and can be effectively used in their intended applications, it is important to have a comprehensive understanding of their quality characteristics and to exercise meticulous control over them. However, while MPs offer potential advantages over conventional systems, it is important to consider their disadvantages and challenges. These include the requirement for specialized equipment, multiple manufacturing steps, and the need for larger quantities of excipients, such as modified-release polymers, which may not be suitable for paediatric populations. The safe use of excipients is a primary concern for the design and development of paediatric formulations, as it is necessary to consider their safety and toxicity.

- **INSERT FIGURE 6 -**

Fig. 6. Schematic representation of commercial MPs drugs.

Examples of commercial MPs for paediatric use, reported in a previous review are reported in **Table 2**[26].

Table 2. Some examples of MPs on the market[26].

- **INSERT TABLE 2 -**

The prilling/vibration technique offers a solution to the unmet needs of paediatric patients by allowing for the creation of MPs. It is important to note that paediatric patients cannot simply be treated as smaller versions of adults, and therapy must be customised to meet the individual needs of each patient. The technique produces highly flexible and versatile formulations[118], eliminating the need to break or split single-unit formulations. This method enables parents to administer the drug accurately without any additional manipulation, ensuring convenient, easy, and reliable administration while reducing the risk of incorrect dosing. The prilling/vibration technique also aims to overcome palatability issues by using excipients that mask the taste. Although there are no commercially available MPs for paediatric use produced using prilling/vibration, this technique is extremely advantageous in the production of MPs compared to those made using conventional techniques and is becoming increasingly popular as a promising alternative to traditional production techniques. There are some examples in the literature of the use of this technique to make multiparticulates suitable for the paediatric age group. In the following work[119], the prilling/vibration/vibration technique was used to produce omeprazole-loaded alginate microspheres that allow age- and weight-specific dosing in children for the treatment of gastro-oesophageal reflux disease. All proposed formulations, due to their specific omeprazole content, appropriate size (1.25 mm) and spherical morphology can be easily swallowed by children and can be administered to paediatric patients of different ages.

MPs can also be used as a paediatric dosage form to mask the inherent unpleasant taste of many drugs, overcoming the obstacles of producing a commercial flavour-masked dosage form and increasing patient compliance. A study[120] used the prilling/vibration technique to develop MPs capable of masking the bitter taste of propranolol hydrochloride, used in the treatment of childhood haemangioma, which does not facilitate children's compliance, especially in liquid formulations currently on the market. The prilling/vibration technique was used to produce MPs encapsulating the drug in a matrix of Eudragit® EPO, with good yields and diameters appropriate for the paediatric population. Electronic tongue measurements revealed the ability of these formulations to mask the bitter taste of the drug so that these MPs could be proposed as new solid oral formulations for use by children. In fact, they showed improved palatability, increased patient compliance by masking an unpleasant taste, increased swallowability, flexible dosing, and a stable and manageable system for storage and transport.

The same technique was used in another work[121] that aimed to develop an oral paediatric formulation of budesonide for the treatment of inflammatory bowel disease. The prilling technique allowed the production of budesonide-loaded MPs able to respond to parallel stimuli that are in the colon, such as pH, transit time and resident microbiota, using polymers able to respond to specific stimuli. Drug release studies in simulated gastrointestinal fluids and faecal media showed the response of the microspheres to each of the different stimuli, confirming the success of the prilling technique of making colonic delivery formulations. Moreover, the MPs, which have an average diameter of less than 655 µm, were flexible and accurate in dosing, easy to swallow, and suitable for oral administration in paediatric patients.

All the studies conducted highlight the great applicative versatility of the prilling/vibration technique to produce MPs that meet both formulation and patient requirements. MPs represent an interesting alternative to conventional solid dosage forms for the administration of drugs to patients with swallowing difficulties, as they are flexible in terms of dosage, ensure easy intake and swallowing, and improve compliance in children.

Although this technique has shown interesting applications in different sectors, from pharmaceuticals to foodstuffs to cosmetics, there are still few studies in the literature in which it is used to produce MPs for paediatric use, although, by the advantages that have been described, it may well be a technique with rapidly growing use in the future.

4. MICROFLUIDICS

The use of microfluidics (MF) technology offers distinct advantages in the production of paediatric formulations, addressing the specific needs of younger patients[122]. In paediatric medicine, where precise dosing is crucial, this level of control ensures accurate drug delivery, reducing the risk of overdosage or underdosage, which can be particularly critical for children. Moreover, MF systems are amenable to scaling down production, which aligns perfectly with the lower dosage requirements for paediatric patients. Additionally, MF platforms can be tailored for the encapsulation of sensitive or hydrophobic drugs, enhancing drug stability, and bioavailability and allowing for the development of innovative paediatric formulations[123]. Overall, microfluidics-based drug delivery systems production offers precision, scalability, and customization, making it a valuable tool in advancing paediatric pharmaceuticals to improve treatment outcomes and patient adherence in the paediatric population.

In detail, MF is a field of science and engineering that deals with the behaviour, manipulation, and control of fluids at the nano- and microscale levels. MF involves the study and application of small volumes of fluids (10^{-9} to 10^{-18} litres) in channels, chambers and devices with dimensions ranging from micrometres (µm) to millimetres (mm)[90]. The first microfluidic device was fabricated in the early 1970s[124], while only at the end of the 1990s MF come to the fore[125]. MF systems are designed to exploit the unique fluid flow behaviour at the microscale, whose Reynold number (Re) is typically low (often less than to 1.0)[126] describing the total presence of a laminar flow rather turbulent and a mixing guided by molecular diffusion. These aspects are considered the basis for controlled and reproducible reactions. Among the wide array of MF flows, the continuous-flow microfluidic operation is the mainstream technique, where the fluid flow is determined by external sources such as micropumps (e.g., peristaltic or syringe pumps) or internal mechanisms (electric, magnetic, or capillary forces). MF can have several applications and can help and boost research in different fields, such as pharmaceutical, biological and medical, as summarized in the following **Table 3.**

Table 3. Summary of principle microfluidic techniques.

- **INSERT TABLE 3 –**

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Several variables can be tuned to tailor the final size and distribution of the nanoparticles (NPs) or MPs, along with their drug-loading capability and batch-to-batch repeatability. These parameters include (i) mixing qualities, (ii) flow rate ratio (FRR), (iii) total flow ratio (TFR), (iv) chip geometry, (v) temperature, nevertheless the (vi) materials employed for the DDSs fabrication.

In depth, as the FRR is increased, larger particles are produced, whilst decreasing the FRR improves the mixing process and reduces particle size. Another aspect that influences the FRR is channel dimensions, which determine the pressure, velocity, and mixing efficiency inside channels; as a result, the FRR should be modified to adjust for channel variations while maximizing NPs and MPs production. One of the most common continuous flow mixing techniques is hydrodynamic flow focusing (HFF)[138].

The chip geometry (**Fig. 7**) (e.g., the size and the shape of the channels) could also significantly affect the M MF based formulations. Among others, Y- and T-shaped microfluidic schemes are generally employed in this regard. A variety of strategies, such as the Tesla[139] structured channel and the herringbone mixer[140], have been developed to achieve high-performance mixing. Indeed, tuning the width and height of microchannels influences fluid residence time and thus reaction kinetics and DDSs fabrication generation[141].

MF can be used for self-assembling formulations by varying the FRR between the aqueous and organic phases, the total flow rate (TFR) of the two phases, the temperature into the devices, as well as the ratio of the various ingredients used to produce formulations.

MF devices can be fabricated by using a range of materials and operating different methods[142]. Early prototypes were generally fabricated from silicon and glass via photolithography and wet etching methods[143]. Subsequently, polymer chips gained attention, principally due to their attainability to mass fabrication. Nowadays, the most common chip material employed is the flexible elastomer poly(dimethylsiloxane) (PDMS)[144].

- **INSERT FIGURE 7 -**

Fig. 7. Representative image of the MF device geometry. Figure licensed under a Creative Commons CC-BY 4.0 license adapted with permission from [145].

4.1. Microfluidic technology for nanoparticles fabrication in paediatric therapies

MF technique exhibits a promising approach in various fields, such as biology, chemistry, and physics, including pharmaceutical and medical applications. The development of paediatric formulations using MF techniques can offer several advantages, such as precise control over particle size, improved drug solubility, enhanced bioavailability, and easier administration for paediatric patients. The paediatric population is a miscellaneous group of patients with a wide array of physiological and developmental differences, specifically in terms of metabolism, organs and tissues, which influence the pharmacokinetics and pharmacodynamics of a drug and its delivery. In the context of the production of paediatric medicines, microfluidic technology offers several advantages over traditional methods, and it can be compared with other competing technologies, as follows: microfluidic devices allow precise control over fluid flow, mixing, and reaction conditions on a small scale[146]; this precision is crucial in the production of paediatric medicines where accurate dosing is essential. Microfluidic systems can be designed for high-throughput production[147], allowing for the rapid screening and optimization of formulations which is particularly valuable in the development of paediatric medicines. MF minimizes the need for large quantities of reagents and solvents, reducing waste and making the process more environmentally friendly[148]. MF platforms can integrate various processes such as synthesis, mixing, and analysis within a single device, streamlining production processes, while traditional methods may require separate steps and equipment for different processes[149]. The parallel nature of microfluidic systems enables the production of large quantities of micro- and nanodevices in a relatively short time, offering high throughput in laboratory settings, which is a step forward to a possible industrial scale out ~~up~~[150,151]. In this scenario, MF technology has the potential to revolutionize the development of paediatric formulations through precise control over the composition and characteristics of the formulation, satisfying the CQAs. This level of control enables the optimization of drug delivery parameters, such as particle size, drug concentration and viscosity, which are crucial for paediatric formulations. MF allows high-throughput screening, providing the rapid screening of multiple formulations and parameters simultaneously, reducing the time and cost associated with traditional

trial-and-error methods[152]. This capability allows scientists to explore various drug combinations and formulations more efficiently. Furthermore, another key point is the tailored drug delivery[153] and, thus, the drug release profile. On that note, MF devices can be designed to mimic the physiological conditions in paediatric patients, such as oral administration or nasal delivery[136]. By replicating these conditions, researchers can better understand the drug's behaviour and optimize its delivery for paediatric sufferers[130]. Moreover, by incorporating specific materials into the formulation is possible to provide the desired controlled or sustained release profiles[154,155]. This can be advantageous in paediatric treatments where the frequency of administration needs to be minimized or specific dosing intervals are required. In this regard, MF offers the potential for age-appropriated medicine[153] by allowing the formulation to be tailored to a specific and individual child's needs. This customization can consider factors such as age, weight, and specific medical conditions, optimizing the therapeutic outcomes[156]. Indeed, MF platforms can provide the means to produce small batches of personalised paediatric formulations with precise dosages and compositions. Additionally, MF can contribute to the development of a simplified administration. For instance, MF systems can be designed to produce liquid formulations with improved taste masking or reduced bitterness, making them more palatable for children. Similarly, MF techniques can aid in the production of oral films, patches, or micro-tablets, which are more suitable for paediatric patients who may have difficulty swallowing conventional solid dosage forms.

The word "nanomedicine" was defined by the European Technology Platform on Nanomedicine (ETPN) as the application of nanotechnology to improve healthcare through the unique bio and physicochemical features of materials at the nanoscale. On the other hand, the EMA defines nanomedicine as the use of nanoscale materials with particular beneficial characteristics, like improved drug targeting and bioavailability, novel therapeutic mechanisms, and nanostructured surfaces or scaffolds for engineered tissues[157,158].

The application of nanomedicine in paediatric medicine has provided innovative approaches to diagnose and treat a wide array of diseases.

Among the most investigated nanoparticles intended for the prophylaxis, diagnosis, and treatment of pathologies emerged lipid-based nanoparticles. Their advantageous characteristics, such as biocompatibility, ease of formulation, and variability of payload, make them the FDA's most highly authorized nanomedicines. In detail, the most extensively researched of these nanosystems in paediatrics are liposomes, and differences in pharmacokinetic parameters between adult and paediatric populations have been observed across transversal attributes[159].

In particular, nanomedicine is the application of nanotechnology in the pharmaceutical and medical fields[160]. In the last two decades, nanosystems have gained more and more attention and they have been hardly investigated as optimal platforms for drug delivery[161]. They can be produced by natural or synthetic materials which significantly affect the properties of the final formulations. These innovative nanovectors include liposomes, polymeric nanoparticles, dendrimers, nanogels and other lipid based nanosystems, such as solid lipid nanoparticles (SLNs) and nanostructured lipid nanoparticles (NLCs), just to cite a few. It was evidenced that, when compared to polymeric nanoparticles and inorganic nanoparticles, the lipid-based carriers are more biocompatible, biodegradable, nonimmunogenic, less toxic and safer[162]. These drug delivery systems have been produced traditionally by bulk method applying the bottom-up or top-down fabrication technique.

In this regard, in recent years, MF techniques have gained significant attention for their ability to precisely manipulate fluids at the microscale level. These techniques offer numerous advantages for creating nanoparticles (NPs), such as enhanced control over size, shape, and composition, as well as scalability and potential for high-throughput production.

APIs included into nanoformulations are also diverse, ranging from chemotherapeutics[163] to gene therapy[164]. The recent COVID-19 pandemic has additionally boosted the application of MFs, with an emphasis on vaccine-based RNA delivery employing MFs as a preferential formulation platform[165–167].

Indeed, the use of nanomedicines has been influencing the way diseases are treated. The primary advancement in paediatric nanomedicine is its use to cancer treatment. According to Yang et al.'s analysis[168], a search conducted on ClinicalTrial.gov on March 11th, 2021, turned up 10 clinical trials specifically made for children utilizing liposome nanocarriers as a treatment for paediatric cancer. The majority of these nanomedicines, as cancer medication formulations (e.g. Doxil, DaunoXome, Myocet, DepoCyt) (Table 4) provide advantages over the "free" medication, such as decreased toxicity and/or increased efficacy[169]. Certain medications, such Abraxane® (paclitaxel), Marqibo® (vincristine sulfate), and Mepact® (mifamurtide), among others, have been assessed and approved for use in children even though the majority of pharmaceuticals

were initially created for use in adults[170]. Furthermore, on March 30th, 2021, the FDA authorized a new indication for daunorubicin and cytarabine (Vyxeos; Jazz Pharmaceuticals) to treat paediatric patients ≥ 1 with newly diagnosed acute myeloid leukaemia (AML). Daunorubicin and cytarabine are a liposomal combination of cytarabine, a nucleoside metabolic inhibitor, and daunorubicin, an anthracycline topoisomerase inhibitor. Based on safety data from two single-arm clinical studies, the AAML1421 study and the CPX-MA-1201 study, as well as efficacy evidence from an earlier clinical trial in adults, the FDA authorized this additional indication in paediatric patients.

Table 4. Nanoparticle formulations in the market. Adapted with permission from [171].

- **INSERT TABLE 4 –**

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As there are currently over ten US Food and Drug Administration (FDA) authorized pharmaceuticals using lipid nanoparticles (LNP) drug delivery systems to deliver therapeutics to illness sites, this is especially relevant to nanomedicines using LNP drug delivery systems.

The current knowledge of LNP-based systems for small molecule release has facilitated the clinical translation of these systems [177]. Specifically, it is well recognized that the microfluidic process is an extremely effective way to produce a variety of LNPs on an industrial scale[177], as demonstrated by the two vaccines that have shown the most promising results in preventing COVID-19 infection consisting of mRNA encapsulated in LNPs: mRNA-1273/SpikeVax by Moderna and BNT162b2/Comirnaty by BioNTech/Pfizer. Both vaccines were granted 'Emergency Use Authorization' by the U.S. Food and Drug Administration (FDA) and, in December 2020, 'conditional approval' by the European Medicinal Agency (EMA)[178].

Table 5. Lipid nanoparticles studied as drug carriers in paediatrics. Adapted with permission from [171]

- **INSERT TABLE 5 –**

In this regard, ease of scaling up and rapid optimization of NP production conditions are two more features of a MF device appropriate for NP manufacturing[150,151]. These MF characteristics enable the transfer from laboratory-scale use to real-world applications and make excellent contributions to NP synthesis and NP-based RNA-delivery technologies. RNA, DNA, ribonucleoprotein (RNP), medications, and other NP-delivery platforms have all benefited from the development of different microfluidic devices that generate LNPs[167]. One such device, Onpattro, is the first RNA-interference therapeutic medicine that has been approved. This represented a crucial aspect and a forward-looking move concerning MF regulatory barriers[186]. Nevertheless, in order for LNP-based treatments to be clinically valuable, they need to be produced via methods that guarantee quality control, regulatory compliance, stability during storage, and compatibility with sterilizing[187].

The successful MF method was first registered by Jahn et al.[188], reporting the production of liposomes.

The main innovation of microfluidics is the ability to transfer the traditional bulk technique to nanometric width microchannels. In this regard, Arduino et al.[189] demonstrate the several advantages of using the MF technique for SLNs production, specifically in terms of size distribution, polydispersity index, and encapsulation efficiency when compared to the bulk method.

Sommonte et al. investigated the only previous applications of MF for the production of biologic-encapsulated APIs[190]. This investigation opens the field to the exploration of paediatric pathologies which do not have already marketed therapies that would require encapsulating-biological formulation. As an example, traumatic brain injury (TBI) is a traumatic condition caused by a forceful bump or blow to the head or body and is the main cause of disability and/or death, occurring with a higher incidence in children and young adults, even in elderly individuals[191]. To date, there are no FDA-approved pharmacological treatments which adequately promote neuroprotection and/or neurodegeneration. MF technique could offer several advantages for this purpose. In this regard, our research group is focusing its attention on the development and optimization of an SLN-based carrier for the delivery and controlled release of a brain growth factor, specifically Brain-derived neurotrophic factor (BDNF). The encapsulation of biologicals into SLNs is a step forward towards the prevention of poor bioavailability, short half-life and capability of overcoming the blood brain barrier. Currently, experiments are undergoing to verify the neuroinflammation activity.

Furthermore, paediatric brain tumours are the third most frequently occurring type of cancer in childhood, the leading cause of childhood cancer-related deaths[192]. Medulloblastomas, low-grade and high-grade glioma, and ependymomas are the most frequent form of cancer in children[192] although metastatic lesions are less common than in adults and approximately more than half of childhood brain tumours are benign. Standard treatments for these diseases include surgery, radiotherapy and chemotherapy, bringing with them all the unwanted drawbacks. These findings demonstrate that paediatric brain tumours are a promising application area for MF based innovative formulations.

The development of a drug delivery system that can be used in clinical cancer therapy requires the optimization of processes to ensure that the finished products are standardized, consistent from batch to batch, scalable, compliant with good manufacturing practice (GMP), and able to be assembled using high throughput techniques. MF has become a potential approach to meet these goals.

Additionally, another pathology with a higher incidence in the first decade of young patients is epilepsy, which is defined as a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition[193]. Brain disorders can result in both epilepsy and comorbidities including cognitive impairment, autism spectrum disorder (ASD) depression/anxiety, sleep disturbances, attention-deficit hyperactive disorder (ADHD), and migraines. Despite paediatric epilepsy being more susceptible to remit than adult epilepsy, administering anti-epileptic medicines to children is problematic due to their faster clearance than adults[194]. Drug resistance is one of the issues associated with anti-epileptic therapy, thus, decreasing the therapy effectiveness[194,195]. Thus, controlled drug delivery systems produced by the MF technique are a promising approach.

Additionally, children's adherence to therapy may be hindered by an unpleasant taste in drugs, particularly a bitter one. For this reason, sensory study of paediatric oral formulations is crucial. A taste masking evaluation is predicated on the idea that the development of nanotechnology formulations has the potential to conceal the bitter taste of the medication[196].

The challenges associated with developing a manageable pharmaceutical form, masking the taste of active pharmaceutical substances, and selecting suitable inputs for this age group are additional considerations that may impact the development of paediatric medications[11,197].

The World Health Organization and the National Institutes of Health both state that developing pediatric formulations should be prioritized for the well-being of children's health, and that factors including excipient safety, formulation palatability, and appropriate dosage form should be considered. Based on this assumption and the knowledge that oral administration is the preferred method for the general paediatric population, Tang et al. [198] developed a paediatric formulation for the treatment of malaria made of stable, fast dissolvable, and primarily pleasant liposomal formulation when taken orally. Mefloquine was put into the liposomal aqueous core utilizing electronic tongue analysis, so that the medication's powerful bitterness was masking. This was the first report of liposomes being employed to get over technological difficulties in medicine taste masking in a flexible solid paediatric formulation. In addition, mice testing the formulation revealed good bioavailability and sufficient stability at room temperature for three months following lyophilisation.

In the pharmaceutical industry, taste masking techniques are frequently employed to improve paediatric patients' adherence to medication therapy. Encapsulation and coating techniques are frequently employed to prevent medications from coming into direct contact with palate, for a solid dosage form, resulting in a reliable flavor-masking system. Anyway, children find it difficult to swallow pills and capsules. On the other hand, sweeteners and flavors are often used in liquid taste-masking systems, even though these adjuvants may cause unfavorable reactions in young patients. Consequently, Fan et al. [196] employed nanotechnology as a substitute for flavors and sweeteners in liquid taste-masking systems. In order to improve patient compliance, conceal the bitter taste of quinine sulphate, and provide a flexible dose scheme based on body weight, a liquid formulation of solid lipid nanoparticles made using a range of surfactants was suggested [199]. Using the Franz Diffusion cell test, the amount of quinine sulphate produced from the solid lipid nanoparticles in simulated salivary fluid (pH 6.8) was used to measure the taste-masking efficacy of the nanoparticles. After 30 minutes, the formulation with poloxamer 188 had the lowest release of all the formulations examined. As a result, a considerable portion of the medication avoids coming into contact with saliva, which suggests that nanotechnology has improved taste-masking effectiveness.

However, several issues should be taken into account when creating a nanomedicine by MF for paediatric use, especially those related to safety and efficacy that may have long-term implications[200]. Research on the

potential effects of environmental nanoparticles exposure on children's development, health, and responsiveness to therapy would also be crucial[201]. Furthermore, studies utilizing nanoparticles in children may be restricted due to ethical concerns about informed consent in this age group for clinical trial enrolment, nevertheless socioeconomic challenges.

4.2. Microfluidic technology for microparticles fabrication in paediatric therapies

MPs are tiny solid or liquid particles with dimensions typically ranging from a few micrometres (μm) to hundreds of micrometres. These particles can be engineered to have specific sizes, shapes, and compositions for various purposes, such as drug delivery, diagnostics, and materials synthesis. Several MF techniques can be employed to formulate MPs: (i) Droplet-based microfluidics, whose MF devices are used to generate and manipulate tiny droplets of a desired material suspended in another immiscible fluid. By controlling the flow rates and the properties of the fluids, researchers can precisely control the size and composition of these droplets, which can subsequently be solidified to form microparticles. (ii) Emulsion-based methods: MF can be employed to create emulsions, which are stabilized mixtures of two immiscible liquids, such as oil and water. These emulsions can be used as templates to create MPs. For example, by introducing a cross-linking agent into one of the phases and then polymerizing it the droplets in the emulsion can be solidified into MPs[202]. (iii) Particle precipitation: MF devices can be designed to mix reactants or solutions under precisely controlled conditions to induce the nucleation and growth of solid particles. The size and properties of these particles can be tuned by adjusting factors like flow rates, reactant concentrations nevertheless reaction times[203]. (iv) Electrospraying, which is a technique that uses an electrical field to break up a liquid into a fine spray of charged droplets. By controlling the parameters, such as the voltage and flow rates, microparticles can be formed from the charged droplets as the solvent evaporates. Electrospraying in MF is a powerful technique used for the controlled generation and manipulation of microscale droplets or charged particles in a liquid phase. This process involves the application of an electric field to a conductive fluid (typically an electrolyte solution) as it flows through a microchannel or capillary. As a result, the electric field induces the formation of a fine aerosol of charged droplets from the liquid stream[204]. Some key features and advantages of electrospray in MF include precise control over droplet size and composition, the ability to encapsulate or manipulate biomolecules, nanoparticles, or cells within droplets, and the capacity for high-throughput experiments. This technique is particularly valuable in the development of microscale assays, drug delivery systems, and lab-on-a-chip devices, where the controlled generation and manipulation of small droplets play a crucial role in achieving precise and reproducible results. (v) MF can also be utilized in 3D printing processes to create MPs layer by layer, offering high precision and control over particle shape and size[205]. MF 3D printing is an innovative technology that combines the principles of MF and 3D printing. It allows for the fabrication of three-dimensional structures with intricate microscale channels and chambers designed for precise control and manipulation of fluids. This approach merges the versatility of 3D printing, which can create complex geometries, with the precision and functionality of MF. In MF 3D printing, materials are deposited layer by layer to build a 3D structure, and during this process, microfluidic features, such as channels and reservoirs, can be integrated seamlessly into the design. This technology finds applications in various fields, including biotechnology, medicine, and chemistry, where it enables the creation of custom-designed MF devices tailored to specific research or industrial needs.

Microfluidic techniques for producing MPs hold great promise for paediatric applications, in particular regarding: (i) controlled release, as microfluidic MPs can be engineered to encapsulate drugs and provide controlled release profiles, which is particularly relevant for paediatric patients where precise dosing and sustained drug release may be critical for therapeutic efficacy and minimizing side effects[206]; (ii) vaccine delivery[207], ensuring efficient immune response with reduced discomfort for the child; (iii) taste-masking and palatability: MF can be employed to encapsulate bitter-tasting drugs within MPs, improving palatability for paediatric patients who may have difficulty swallowing or are sensitive to taste; (iv) paediatric oncology[208], MPs can be designed to deliver chemotherapy drugs with high precision to tumour sites, minimizing systemic exposure and reducing side effects in paediatric oncology patients; (v) inhalable formulations, providing an efficient respiratory drug delivery: MF can be applied to develop MPs suitable for inhalation, facilitating respiratory drug delivery for paediatric patients with conditions like asthma or respiratory infections[209]; (vi) diagnostic applications, by producing biosensing MPs with specific diagnostic functionalities, aiding in the early detection of diseases in paediatric patients[210]; (vii) paediatric nutrition[211], MPs can be designed for encapsulating and delivering essential nutrients, vitamins, or supplements, addressing specific nutritional needs in infants and children; (viii) minimizing invasive procedures[212], MPs with sensing capabilities can be

developed through MF for minimally invasive monitoring of biomarkers or physiological parameters in paediatric patients, reducing the need for invasive practices.

These are just a few examples of how microfluidic techniques can be employed to prepare MPs with precise control over their properties. Through careful microscale manipulation of multiphasic flows, MF has become a potent method for producing polymeric MPs with customized shapes and compositions. It is possible to design engineered biopolymer-based MPs with well-defined physicochemical properties that are capable of enabling efficient delivery of therapeutics, 3D cell culture, and biomolecule sensing. This is made possible by the synergistic combination of materials chemistry afforded by biopolymers and precision provided by microfluidic capabilities[213]. In conclusion, MF systems offer advantages such as high throughput, reproducibility, and the ability to work with small sample volumes, making them valuable tools in various scientific and industrial applications.

5. Future perspectives: biological and genetic therapy

The use of these advanced technologies in paediatric therapy could potentially transform the treatment of a wide range of genetic disorders and chronic diseases. 3D printing, prilling, and microfluidic technologies have the potential to be key tools in the design and manufacture of gene and biologic therapies tailored for paediatric patients.

The 3DP technique has recently attracted interest due to the possibility of generating biological drugs[214]. Biological drugs, or biologicals, are classified as molecules obtained through biotechnological processes engineered into a living system, such as bacteria, plants, or animal cells (i.e., therapeutic peptides and proteins, monoclonal antibodies, and vaccines). These biologicals are intended to regulate various physiological processes to treat or manage the progression of various disorders, including hormone dysregulation, tumours, inflammatory bowel diseases (IBD), and rheumatoid arthritis[215,216]. There is an increasing volume of evidence suggesting that early use of biologicals can improve rates of remission and disease complications, which is why there is a need to formulate biologicals with customised dosages for paediatric patients[217,218]. Indeed, 3D printing is being used for the creation of multilayer structures of human skin cells[219] or the creation of vascularised tissues containing different cell populations[220], suggesting the potential of this technique in the customisation of tissues, biomaterials, and biological substrates useful for medical application or paediatric therapy.

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. However, microencapsulation is emerging as an innovative solution to solve these problems by developing new oral delivery systems. Microencapsulation of cells, including mesenchymal, embryonic, and induced pluripotent stem cells, offers a customised approach for effective treatments. This technology provides protection and stabilisation of cells from external factors and the immune system while enabling the controlled release of therapeutic agents. Promising clinical results indicate the beneficial potential of microencapsulation in the transplantation of isolated cells and the repair of organs such as the heart, liver, and brain. This approach shows efficacy in the treatment of type I diabetes, where a regulated release of insulin in response to the patient's metabolic needs is crucial[221]. However, despite the promising results many studies still need to be performed to translate these important findings to the paediatric population.

In the context of gene therapy, MF techniques have demonstrated several applications for gene transfection and the production of gene carriers. The target cell, the external genetic material, and the transfection stimulation may all be more precisely controlled in space and time in the microfluidic environment. Traditional transfection methods entail randomness, which is eliminated by MF. It is possible to better manage the strength and duration of the transfection stimulus that a specific cell experiences, as well as to be more confident of the degree to which a cell is exposed to the external genetic material. These capabilities might make it possible to create transfection circumstances that are either ideal or nearly ideal, which would raise transfection efficiencies. Since no cell is exposed to harmful transfection stimuli above and beyond what is required to induce transfection, such conditions can also result in higher cell viability[164].

LNPs can also be produced for the delivery of plasmid DNA and nanomedicine-based gene therapy[222].

The lipid nanosystems also protect against the enzymatic degradation of antibodies and allow a sustained release of antibodies[223]. Additionally, antibody encapsulation might be an effective way to prolong the time between doses, improving therapy convenience[224]. According to research by Abrishami et al., bevacizumab concentration in the vitreous was above therapeutic concentration for at least 42 days following the intravitreal delivery of nanoliposomes containing bevacizumab[225]. It essentially proves that nanoliposomes are delivery vehicles with the capacity to prolong the interval between doses. Furthermore, antibody nanoencapsulation may enhance cellular absorption and provide defense against lysosomal digestion[226].

Among new emerging treatments, cell therapy is a new modality. Cells must successfully target the illness site for them to be effective nanomedicine carriers. To have a therapeutic effect on CNS illnesses, they must also be able to cross the blood-brain barrier. There is an inflammatory component to peripheral diseases, and many neurological conditions in particular, which can actively attract macrophages. Additionally, it has been noted that macrophages carrying nanoparticles travel to regions affected by cancer, spinal cord injuries, cerebral ischemia, and myocardial infarction[227]. In this context, a potential and alternative treatment in cancer childhood therapy could be represented by the production through the MF technique of cell membrane (CM)-modified nanoparticles (NPs), a promising biomimetic platform that enables longer blood circulation times, enhanced tumour targeting, and decreased immunological clearance. MF approaches have shown to be definitely highly effective in producing biomimetic nanoparticles when compared to traditional methods. Sensitive biomolecules are known to be gently treated using MF techniques, which reduce heat and shear stress that can jeopardize the integrity of the molecules[228].

CONCLUSIONS

In conclusion, the detailed analysis of 3D printing technologies, prilling/vibration, and microfluidics in the context of paediatric dosage form manufacturing has revealed a rapidly evolving landscape in this field. These innovations exhibit the significant potential to improve the efficacy, safety, and personalisation of therapies for paediatric patients by addressing the unique challenges associated with their specific needs. The implementation of such technologies involves a collaborative effort between the pharmaceutical industry, academia, regulatory authorities, and healthcare professionals. All the techniques described in this review can be considered for future industrial scalability. To date, prilling/vibration techniques result suitable for preliminary pilot scale studies aimed at assessing time, cost, and scalability factors useful for implementing the technique in industrial processes. The 3D printing and microfluidic technique, on the other hand, already presents a real possibility of industrial scalability proven by the extensive use in industrial production processes documented in this review. Despite these prospects, all the techniques presented suffer from a lack of regulation and validation processes that would extend their application. These measures would ensure that production processes could be validated and that formulations obtained by these new techniques could meet the required safety and efficacy standards and be readily available for the needs of paediatric patients. However, the continuous development of these technologies is necessary to exploit the numerous advantages presented in the production of customised pharmaceutical forms in terms of shape, dosage, and release kinetics. All the proposed techniques ensure the production of drugs based on active pharmaceutical ingredients and biotechnology products, improve and speed up process mechanics, and reduce the possibility of human error. The successful integration of these techniques in large-scale pharmaceutical production will depend on achieving a balance between customization and standardization, managing costs, and promoting continuous technological innovation. For this reason, in the coming years, there will likely be more progress and breakthroughs in this field, seeking to enhance the well-being of paediatric patients and guarantee fair access to the most advanced age-appropriated and accurate pharmacological therapies.

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Conflict of interest

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FIGURES

Fig. 1. Schematic representation of FDM (a), Direct ink writing (b), inkjet printing (c), stereolithography (d) and selective laser sintering (e) 3DP techniques. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [53].

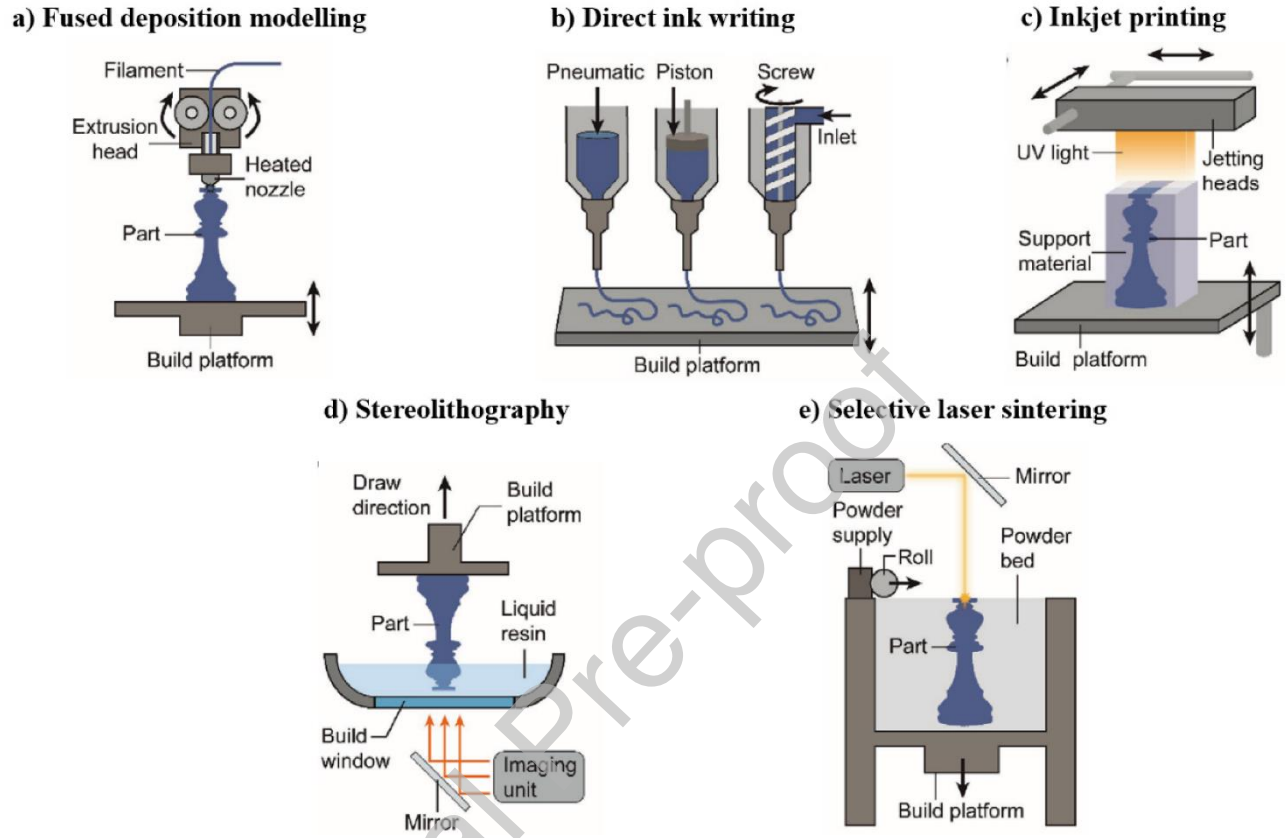


Fig. 2. Schematic representation of 3DP PAM extrusion systems. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [60].

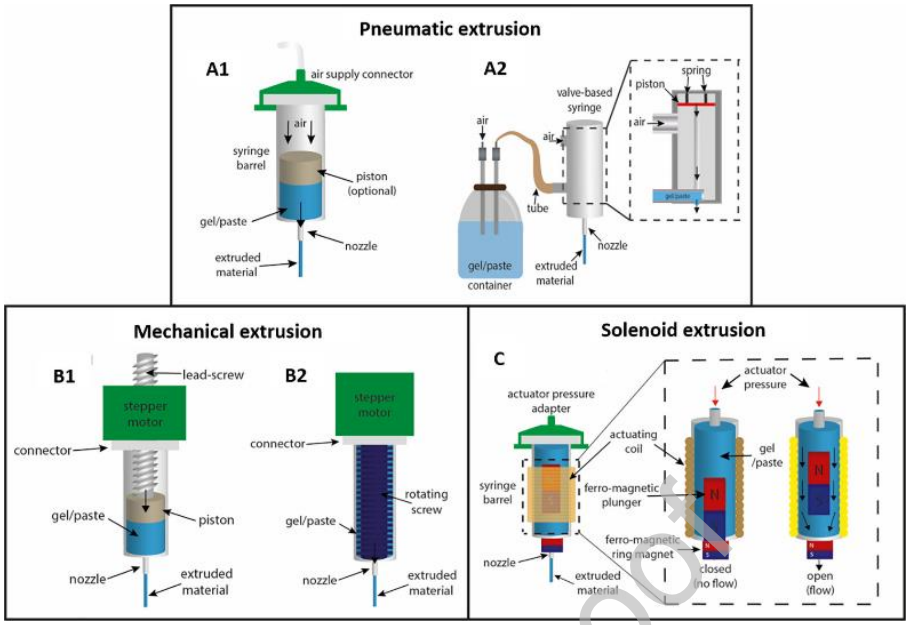


Fig. 3. Examples of chewable tablets with different shape and composition. Figure 2A licensed under a Creative Commons CC-BY-NC-SA license adapted with permission from [48]. Figure 2B and 2C licensed under a Creative Commons CC-BY 4.0 license with permission from [71].

Fig. 4. Graphical schematisation of the most commonly used techniques for obtaining MPs. Figure licensed under a Creative Commons CC-BY 4.0 license, adapted with permission from [89–93]

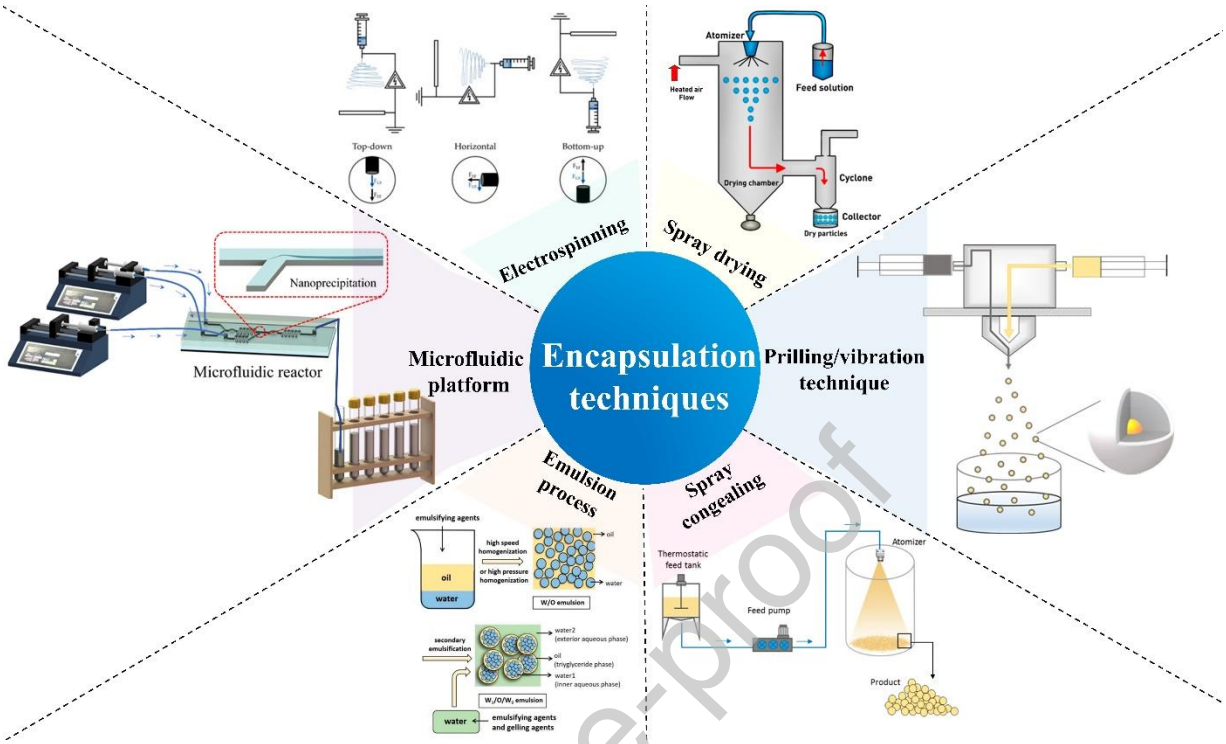
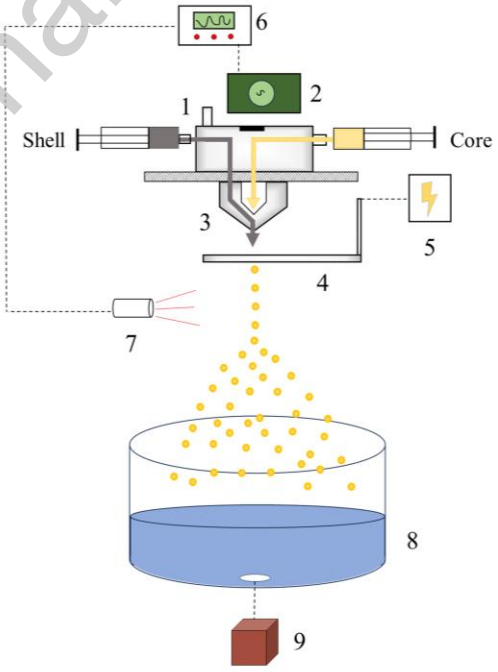


Fig. 5. Schematic representation of the microencapsulation process.



1 Microcapsules production unit
2 Vibration unit
3 Concentric nozzle
4 Electrode
5 Dispersion control
6 Vibration control
7 LED
8 Consolidation bath
9 Magnetic stirrer

Fig. 6. Schematic representation of commercial MPs drugs.

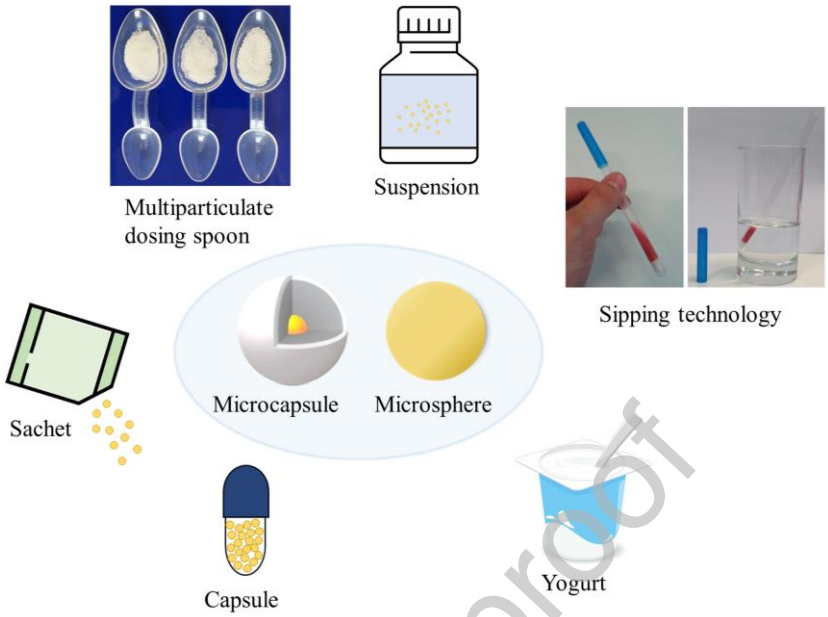
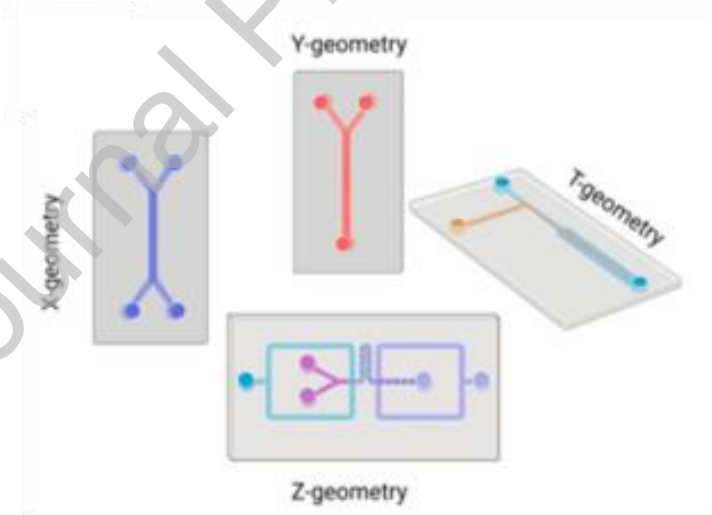


Fig. 7. Representative image of the MF device geometry. Figure licensed under a Creative Commons CC-BY 4.0 license adapted with permission from [137].



TABLES

Table 1. Some examples of paediatric oral dosage forms on the market[26].

	Drug Name	API	Treatment indications
Mini - Tablets	Desitrend®	Levetiracetam	Adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy (from 1 month)
	Lamisil®	Terbinafine hydrochloride	Treatment of tinea capitis (from 4 years)
	LPV/r pellets	Lopinavir and ritonavir	Treatment of HIV-1 infection (from 3 months)
	Orfiril®	Sodium valproate	Generalized seizures and partial seizures in epilepsy (from 10 years)
Chewable Tablets	Isentress®	Raltegravir	Antiviral treatment against HIV
Orodispersible Films	Setofilm® ZUPLENZ®	Ondansetron	Management of chemotherapy-induced nausea and vomiting (from 6 months), prophylaxis, and treatment of postoperative nausea and vomiting (from 4 years)
	EXSERVAN™	Riluzole	Amyotrophic lateral sclerosis (adults only)
	SUBOXONE®	Buprenorphine and Naloxone	Opioid Substitution Therapy (adults only)
	BELBUCA™	Buprenorphine	Management of severe pain (adults only)

Table 2. Some examples of MPs on the market[26].

	Drug Name	API	Preparation	Use
	Sustiva®	Efazirenz	Open capsule(s) and add contents to 1-2 teaspoons of soft food such as applesauce, grape jelly, yoghurt, or 10 mL of infant formula in a small container. Administer with a spoon or syringe.	Antiviral
	Cholbam®	Cholic acid	Capsules may be opened, and their contents mixed with 15-30 mL of infant formula or	For the treatment of bile acid synthesis disorders

Sprinkle capsules			expressed breast milk. For younger children, use breast milk, while for older children and adults, opt for soft food like mashed potatoes or apple puree to conceal any unpleasant taste.	
	Nexium®	Esomeprazole magnesium	Add the contents of a capsule to applesauce, then administer.	For the treatment of gastroesophageal reflux disease (GERD)
	Tasigna®	Nilotinib HCl	Contents of each capsule dispersed in 1 teaspoon of applesauce.	For the treatment of Philadelphia chromosome positive chronic myeloid leukemia
	Tamiflu®	Oseltamivir phosphate	Open the capsules and mix with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water).	Antiviral
	Adderall XR® or Metadate® and Ritalin®	Metilfenidate and methylphenidate hydrochloride	Open capsule(s) and sprinkle on apple puree or baby food.	For attention deficit hyperactivity disorder (ADHD
	AcipHex® Sprinkle™	Rabeprazole sodium	Open capsule(s) and add contents to a small amount of soft food such as applesauce, baby food or yogurt, or a small amount of infant formula, apple juice in a small container. Administer with a spoon or syringe.	For the treatment of gastroesophageal reflux disease (GERD)
Oral Powder	Reyataz®	Atazanavir sulfate	Mixed with food such as applesauce or yogurt or infant formula.	Antiviral
	Viread®	Tenofovir disoproxil fumarate	Use the measuring spoon to measure the dose that is then added to the soft baby food.	Antiviral
	Creon® Micro	Pancreatin	Use the measuring spoon to measure the dose that is then added to the soft baby food.	Exocrine pancreatic insufficiency due to cystic fibrosis
Oral Granules	Xuriden™ and Vistogard®	Uridine triacetate	Administer dose with soft food (applesauce, pudding, or yogurt) or in milk or infant formula within 30 min.	For the treatment of hereditary orotic aciduria
	Orkambi®	Lumacaftor + ivacaftor	Mixed contents of a packet with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 h with fat-containing food.	For the treatment of cystic fibrosis

Table 3. Summary of principle microfluidic techniques.

Technique	Characteristics	References

Microfabrication	MF devices are typically fabricated using microfabrication techniques borrowed from the semiconductor industry. This involves photolithography, soft lithography, and micro-milling to create microchannels, chambers, and other structures on a chip	90
Flow Control	MF devices allow precise control over fluid flow rates and directions. Techniques like pressure-driven flow, electroosmotic flow (EOF), and electrophoresis are used to manipulate fluid movement	127
Mixing and Reaction	Due to the small scale of microfluidic channels, diffusion is often slow. Various methods, such as active mixing using mechanical structures or passive mixing using chaotic advection, are employed to enhance mixing and facilitate reactions	128
Separation and Sorting	MF enables the separation and sorting of particles, cells, or molecules based on their physical or chemical properties. Techniques like dielectrophoresis, hydrodynamic focusing, and inertial microfluidics are used for this purpose	129
Lab-on-a-Chip	MF devices integrate multiple laboratory functions onto a single microfluidic chip. This can include sample preparation, mixing, separation, and detection, enabling quick and efficient analysis	130
Single-Cell Analysis	Mf allows to isolate and analyse individual cells, enabling a deeper understanding of cellular heterogeneity and behaviours	131
Droplet Microfluidics	MF technique involves generating and manipulating tiny droplets of fluids in microchannels. It has applications in high-throughput screening, drug encapsulation, and single-cell analysis	132
Electrophoresis	In MF, electrophoresis can be used to separate charged particles, such as DNA fragments or proteins, based on their size and charge	133
Electrochemical Detection	Electrochemical sensors integrated into microfluidic devices enable real-time monitoring of chemical reactions and analyte concentrations	134
Biosensing	MF is used to create sensitive biosensors for detecting specific molecules or pathogens, with applications in medical diagnostics and environmental monitoring	135
Organ-on-a-Chip	MF systems aim to replicate the functions of organs by creating microfluidic devices that mimic the physiological conditions and interactions present in the body	136
Synthetic Biology	MF is used to create controlled environments for studying and engineering biological systems at the cellular or molecular level	137

Table 4. Nanoparticle formulations in the market. Adapted with permission from [171].

Brand Name	Drug	Approval	Composition	Pediatric Use/Indication	Reference
Abraxane®	Paclitaxel	2005	Natural polymer: albumin	Solid tumours	172
Marqibo®	Vincristine sulfate	2012	Sphingomyelin:Cholesterol (60:40)	Lymphoblastic leukaemia	173
DepoCyte®	Cytarabin	1999	Cholesterol:Triolein:Dioleoil phosphatidylcholine: Dipalmitoyl phosphatidyl glycerol (11:1:7:1)	Leptomeningeal dissemination	174
DaunoXome®	Daunorubicin	1996	Distearoyl phosphatidylcholine: Cholesterol(2:1)	Acute myeloid leukaemia	173

Doxil®	Doxorubicin	1995	Hydrogenated soybean phosphatidylcholine:Cholesterol:PEG 200-DSPE (56:39:5)	Hodgkin lymphoma	[175]
Myocet®	Doxorubicin	2000	Phosphatidylcholine: Cholesterol (55:45)	Non-Hodgkin lymphoma	[175]
Mepact®	Mifamurtide	2009	Dioleoyl-sn-glycero-phosphoserine:Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine(3:7)	Osteosarcoma	[173]
Vyxeos®o CPX35	Daunorubicin/Cytarabine	2017	1,2-Distearoyl-sn-glycero-3-phosphocholine:1,2-distearoyl-sn-glycero-3-phospho- (1-rac-glycerol):Cholesterol (7:2:1)	Acute myeloid leukaemia	[176]
AmBisome®	Amphotericin B	1997	Hydrogenated soy phosphatidylcholine: Cholesterol: Distearoyl phosphatidylglycerol (2:1:0.8)	Systemic fungal infections	[173]

Table 5. Lipid nanoparticles studied as drug carriers in paediatrics. Adapted with permission from [171]

Drug	Composition	Pediatric Use/Indication	Reference
Vincristine sulfate	Liposome based on Sphingomyelin:Cholesterol (60:40)	Lymphoblastic leukaemia	[173]

Cytarabin	Liposome based on Cholesterol:Triolein:Dioleoil phosphatidylcholine: Dipalmitoyl phosphatidyl glycerol (11:1:7:1)	Leptomeningeal dissemination	[174]
Daunorubicin	Liposome based on Distearoyl phosphatidylcholine: Cholesterol (2:1)	Acute myeloid leukaemia	[173]
Doxorubicin	Pegylated liposomal based on Hydrogenated soybean phosphatidylcholine:Cholesterol:PEG 200-DSPE (56:39:5)	Hodgkin lymphoma	[175]
Doxorubicin	Non-pegylated liposomal composed by Phosphatidylcholine:Cholesterol (55:45)	Non-Hodgkin lymphoma	[175]
Mifamurtide	Liposome based on Dioleoyl-sn-glycero-phosphoserine:Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (3:7)	Osteosarcoma	[173]
Daunorubicin/Cytarabine	Liposome composed by 1,2-Distearoyl-sn-glycero-3-phosphocholine:1,2-distearoyl-sn-glycero-3-phospho- (1-rac-glycerol):Cholesterol (7:2:1)	Acute myeloid leukaemia	[176]
Amphotericin B	Liposome based on Hydrogenated soy phosphatidylcholine: Cholesterol: Distearoyl phosphatidylglycerol (2:1:0.8)	Systemic fungal infections	[173]
Edelfosine/methotrexate	Lipid Nanoparticle based on Precirol® ATO 5 and Tween® 80	Osteosarcoma	[179]
Doxorubicin	Precirol® ATO 5, triethanolamine, oleic acid, Tween® 80 and EDTA	Osteosarcoma	[180]
Hydrochlorothiazide	Solid lipid Nanoparticle based on hydroxylpropyl-beta-cyclodextrin, Precirol® ATO5 and Pluronic® F78	Hypertension	[181]
Hydrochlorothiazide	Nanostructured Lipid Carrier based on Precirol® ATO5, Tween® 80, Tween® 20 and castor oil	Hypertension	[182]
Hydrochlorothiazide	Solid lipid nanoparticle and nanostructure lipid carrier based on Precirol® ATO5, Transcutol® HP, Gelucire® 44/14 and Pluronic F68 or Tween® 80	Hypertension	[183]
Lopinavir/Ritonavir	Nanocapsule containing Oleic acid and-α- tocopheryl polyethylene glycol 1000 succinate and Aeropearl® 300	Human immunodeficiency virus (HIV)	[184]
Gemcitabine/Edelfosine	Nanoassembly based on squalenic acid and ether lipid	Osteosarcoma and neuroblastoma	[185]

Graphical Abstract

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: