A review on the colours, flavours and shapes used in paediatric 3D printed oral solid dosage forms

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Abstract:

Objectives: This review aims at gleaning the currently available research reports that relate to 3D printlets for paediatric patients, and especially the excipients used to produce various colours, flavours, shapes and sizes.

Methods: A thorough literature review on paediatric 3D printed oral solid dosage forms, focusing on the use of colours, flavours and various shapes/dimensions, was conducted with an adjusted time frame between 2017 and 2022.

Key findings: 3D printlets for paediatric population include the chewable dosage forms (including solid forms and the soft forms or gummies), the swallowing dosage forms, and the orodispersable dosage forms (printlets or films). Researchers have tested many colours, flavours, shapes and dimensions for the chewable formulations production using pectin and gelatin to create gummies or chocolate and cereals. Scientists have also used many methods and excipients to produce printlets with various colours, flavours, shapes and small sizes (minitablets or minicaplets) for the swallowing dosage forms. Concerning the orodispersables, the research was rather limited.

Conclusions: Compared to conventional oral dosage form manufacturing processes, 3D printing techniques use a different approach. More specifically, these techniques can provide personalisation of dose, shape, size, taste, colour and appropriate drug release rates, which is of paramount importance especially for paediatric patients. With the correct excipients the printlets can serve as ideal dosage forms candidates for the treatment of the paediatric population.

1. Introduction

The oral route of drugs' administration is preferable to patients and clinicians because it is the cheapest, easiest and most convenient way (1,2). Furthermore, most of the drugs can be administered orally with various dosage forms, such as chewable formulations, liquids, tablets and capsules. Notwithstanding their advantages, solid and liquid dosage forms still have some limitations; the swallowing difficulties coming with the solid forms for paediatrics and geriatric patients and the stability and dosing errors of liquid forms (3–6). On the other hand, chewable formulations, like lozenges, gummies, gums and chewable/orodispersable tablets and films, are earning attention because they are easy to administer, safe and they do not have any stability issues.

Regarding the target population of chewable tablets, it has been appeared that 1 in 11 patients has difficulties in swallowing tablets and capsules, which is a significant percentage that health professionals do not give the necessary attention (6). Patients suffering from dysphagia, have problems because the swallowing process is disrupted after swallowing solid or liquid drugs. The same is true with the geriatric population, as with ageing the swallowing of tablets becomes annoying, impacting obedience to treatment. As far as children is concerned, they cannot swallow solid tablets and this heterogeneity from the adults is not taken into consideration, resulting to be considered, as "therapeutic orphans" (7). Children need personalisation in their treatment to avoid lower dose or overdose. Characteristic is a clinical trial that asked children between 4-11 years to select the form of their treatment and 79% of them asked for chewable tablets (8).

Taking all of the above into consideration, chewable formulations can be a proper alternative. The use of 3D printing techniques can provide personalisation of dose, shape, taste and appropriate release rates from the produced formulations, which is of great importance for paediatric patients (9,10). Chewable formulations, like lozenges, gums, gummies, chewable tablets, are safe, easy to administer, and they do not have stability problems (Figure 1). The semi-solid extrusion 3D printing technique (SSE 3DP) can be used to produce personalised chewable formulations with various size shapes and flavours (Figure 2) (11,12). The jelly-like formulations are the most famous to be 3D printed, as they have the capability to adjust the formulation's rheological properties, like texture and viscosity (13,14). Generally, chewable formulations are not restricted by the size because they are developed to be chewed before swallowed. Additionally, they can increase the drug's bioavailability by avoiding the first-pass metabolism from the gastrointestinal tract, as some of the drugs are disintegrated and dissolved in the mouth and absorbed from the buccal cavity. Last, there is no need for water to be administered making them a convenient and easy way to administer drugs.

Figure 1: Examples of chewable formulations

Figure 2: Examples of flavours used in 3D printlets

As for the disadvantages, occasionally it is hard to fill chewable formulations with drugs that they have unpleasant taste, e.g. bitter, and pungent, thus demanding the addition of large amounts of flavouring agents and sweeteners. Moreover, in some occasions, patients damaged their teeth due to the excessive hardness of the tablet or faced an oesophageal irritation. Last, chewable tablets are hygroscopic and they have to be stored in a dry place in air-tight containers (15).

Orodispersible films (ODFs) are administered without water, thus increasing patients' acceptability. The preparation of ODFs, using SSE 3DP, can simultaneously rid the patient of the difficulty of swallowing and adjust the dose to the patient's needs (16). Otherwise, the patient needs to cut the tablets randomly, thus compromising the right administration dose. Using ODFs, the use of oral solutions is limited avoiding the dose errors that come with their use (17). Furthermore, ODFs can also be used to psychiatric patients that are non-adherent. They cannot get them out of the mouth on purpose easily and do not cause choking after the administration (18).

2. Methods

A high-quality literature review on paediatric 3D printed oral solid dosage forms, focusing on the use of colours, flavours and various shapes/dimensions, has emerged. Two main databases (Google Scholar and Science Direct) were used for a wide-range search of the topic. Examples of the keywords used in the search were: 3D printed paediatric tablets, 3D printed oral dosage forms, colours and flavours in 3D printing paediatric formulations, etc. Significantly, the search "3D printed oral paediatric AND flavours" with an adjusted time frame of 2017 to 2022, yielded 9420 articles in Google Scholar and 63 articles in Science Direct. Only research articles were selected from this set and duplicates were removed. In addition, studies on non-oral dosage forms or studies on non 3D printing production methods were excluded. Studies without sufficient data, on the excipients used, were also omitted and the final number of articles, which are thoroughly analysed in the present Results and Discussion section, was 28.

3. Results and Discussion

As already mentioned, after a widespread literature review, 28 research articles were carefully selected and analyzed to draw some conclusions regarding the excipients used and the printing methods that affect the production of paediatric 3D printed oral dosage forms. To this end, 3 summary Tables were prepared and the studies were grouped mainly by dosage form. More in particular, Table 1 refers to 3D printed paediatric chewable dosage

forms, while the studies in Table 2 relate to paediatric swallowing dosage forms. Last, Table 3 refers to 3D printed paediatric orodispersable printlets and films. The release behaviour was reported as indicated by the author(s). In the cases, where the author(s) did not fully characterize the release rate, the following rule was applied: if the drug release was ≥ 75% within 30 min, the profile was characterized as immediate. In all other cases, the release profile was characterized as modified. Furthermore, the studies were classified by the printing method [e.g., hot melt extrusion (HME), fused deposition modelling (FDM), binder jet printing (BJP), color jet printing (CJP), direct powder extrusion (DPE), etc.]. In addition to the active ingredient, the Tables also included the main excipients, flavouring and the colouring agents used, the printed shapes and dimensions.

Table 1: Overview of the investigated key attributes of the immediate released 3D printed paediatric chewable formulations (solid dosage forms and soft dosage forms/gummies)

Chewable dosage forms

Chewable dosage forms are promising formulations for the treatment of pediatric patients. Through the last five years, many research groups were involved with 3D printing chewable formulations for children. Zhu *et. al*, 2022 (19), Chachlioutaki *et. al*, 2022 (20), Tabriz *et. al*, 2022 (21), Tagami *et. al*, 2021 (22), Tabriz *et. al*, 2021 (23), Chatzitaki *et. al*, 2021 (24), Karavasili *et. al*, 2020 (25), Januskaite *et. al*, 2020 (8), Herrada-Manchon *et. al*, 2020 (26), Goyanes *et. al*, 2019 (27), Rycerz *et. al*, 2019 (28), Scoutaris *et. al*, 2018 (29) and Karavasili *et. al*, 2022 (30), are amongst them. The main printing techniques, that were employed are the SSE and the HME coupled with FDM.

Chachlioutaki *et. al* (20) used paracetamol as API, Tabriz *et. al* (21) ibuprofen, while Karavasili *et. al* (25) and Rycerz *et. al* (28) studied both paracetamol and ibuprofen, as APIs for chewable paediatric 3D printed formulations. All four research groups used the SSE printing technique. Chachlioutaki *et. al* (20) and Karavasili *et. al* (25) produced chocolate-based formulations. The use of chocolate is important, as it increases children acceptance of dosage forms (25). Chachlioutaki *et. al* (20) constructed formulations of cube shape in various dimensions. As it seems from the linear regression analysis of the paracetamol content in the 3D printed formulations, there are formulations with acceptable dose for children (120-500 mg) (20). As for the release, the dosage form with dimensions (mm): 15 x 15 x 10, showed immediate release in pH 5.8 (20). Karavasili *et. al* (25) chose to produce formulations of various designs and dimensions, which were possible to be likeable to children. As for the release, in gastric simulated fluids (pH: 2.0), paracetamol formulations showed immediate release, while ibuprofen formulations modified release (25). In simulated saliva fluid (pH: 7.0), paracetamol exhibited a release of 22.86%±1.81% and ibuprofen of 36.41%±4.7%, within two minutes (25). Ibuprofen shows a more rapid release than paracetamol, in simulated saliva fluid, and the opposite occurs in the gastric simulated fluid (25). Because of the high permeability and low aqueous solubility of ibuprofen, the rapid and high dissolution in the simulated saliva fluid helps ibuprofen to be readily available for absorption in the oral cavity and across the gastrointestinal tract during

swallowing (25). Tabriz *et. al* (21) produced tablets of the same diameter, but of different composition, as each preparation had a different excipient (soluplus, polyvinylpyrrolidone VA-64, Eudragit EPO), and of different infill (40% and 60%). Each tablet consists of 100 mg ibuprofen (21), which is children-appropriate. The dissolution media used had pH 1.2 and 7.4. From all the preparations, only the tablet with Eudragit EPO and infill 40% showed immediate release at pH 1.2, but the concentration in the dissolution media dropped significantly following the initial drug release due to the crystallization of ibuprofen. On the other hand, modified release was achieved when ibuprofen was used with Eudragit EPO, with infill 40% and 60% in pH 7.4, when ibuprofen was used with polyvinylpyrrolidone VA-64 with infill 40% in pH 1.2, when ibuprofen was used with polyvinylpyrrolidone VA-64 with infill 40% and 60% in pH 7.4, when ibuprofen was used with soluplus with infill 40% in pH1.2 and when ibuprofen was used with soluplus with infill 40% and 60% in pH 7.4. Rycerz *et. al* (28) produced lego™ brick-shaped formulations with different printing patterns (25 %, 50%, 75%, 100%, 200%, 300%) and different colourings. The dimensions (mm) were 20 x 29.52 x 0.45, but for the 25%, 50%, and 75% printing patterns, the designs had identical X and Z dimensions, whilst the Y axis was 8.1, 15, or 22.5 mm, respectively (28). The shape, the dimensions and the colour of formulations made them more friendly to the children. The doses for paracetamol for printing patterns 25 %, 50%, 75%, 100%, 200% and 300% are 16.1 ±2.7, 61.7± 5.1, 77 ± 12.2, 116.7 ± 7.0, 259.4±16.8 and 329.8±6.4, respectively and for ibuprofen are 12.1 ±1.0, 44±1.9, 77 ±4.0, 107.4 ±12.1, 260.3±23.6 and 411.9 ± 19.2, respectively, which are appropriate for children (28). As for the release, a dual dosage form with 80 mg ibuprofen and 200 mg paracetamol was tested at pH 7.2. Thus, both APIs showed modified release (28). Both paracetamol and ibuprofen were released at a similar rate despite the relatively higher solubility of the first compared to the latter at the intestinal pH. This may be due to the slow dissolution of the locust bean gum, a galactomanon that acts as a gel former in the embedded phase (28).

Other research groups that used SSE technique for chewable pediatric formulations are: Zhu *et. al*, 2022 (19), Tagami *et. al*, 2021 (22), Chatzitaki *et. al*, 2021 (24), Januskaite *et. al*, 2020 (8), Herrada-Manchon *et. al*, 2020 (26) and Goyanes *et. al*, 2019 (27). Zhu *et. al* (19) produced chewable dosage forms of propranolol in four different shapes, which could help with children acceptance. The orange flavouring and carmine as colourant could also facilitate pediatric patients' compliance. *γ*-Aminobutyric acid, ferulic acid, as common bitterness inhibitors, and sucralose could also help to improve the taste of the formulations (19). Moreover, the doses are 1.0, 2.0, 2.5 and 5.0 mg, which are acceptable for children. As for the release in personalised formulations, it seems that they showed immediate release, with the 5.0 mg formulation showing the slower release (19). Tagami *et. al* (22) made chewable formulations of lamotrigine in different shapes. The variety of designs, the use of colouring and the use of reduced starch syrup, as sweetener, increases the compliance in paediatric population (22). More in particular, the researchers in this study used monascus pigment for red colour, red beet pigment for pink, spirulina algae for blue, gardenia for yellow, mix of gardenia yellow and blue pigments to achieve green colour, purple sweet potato for purple, grain of gramineous plants for brown, and bamboo charcoal for black colour. Furthermore, the doses, which were below 1 mg and the dimensions, were

appropriate for pediatric patients. Also, the dosage forms showed immediate release at pH 1.2 and HPMC may have more impact on the release rate than gelatin (22). Chatzitaki *et. al* (24) produced starch-based dosage forms of isoniazid in different shapes, and colouring, which were child-friendly. Moreover, based on the linear regression analysis, performed between isoniazid content and increasing numbers of printed layers, the doses of formulations were appropriate for young patients (24). As for the release, the formulations showed immediate release at pH 1.2 (24). Januskaite *et. al* (8) made cylinder-shaped dosage forms without APIs in order to assess young patients visual preference of printlets. Semi-solid printlets were the only chewable and included yellow colouring and lemon flavouring. Although their appearance was not likeable by most children, when the young participants learned that those printlets were chewable, many of them changed their mind and liked them. Herrada-Manchon *et. al* (26) studied formulations with ranitidine hydrochloride in four different shapes. Because of the homogenous and bright colouring, these chewables were very likely to be accepted from paediatric patients (26). Apart from appearance, the strawberry essence and the sweetener were important for children acceptance. Furthermore, the measured doses of formulations were 32.15 ± 1.19 and 26.24 ± 1.43, which are appropriate for children (26). Concerning the release in purified water, it seemed that the existence of corn starch lead to modified release, whilst its absence to immediate release (26). The reason for this could be the gelatinization of corn starch, where gelatinized starch formed a more closely packed gel structure that acts like a more resistant barrier to drug release (26). Goyanes *et. al* (27) produced cylindric-shaped dosage forms with isoleucine, as API. The variety of colourings and flavourings is important in order to ensure children acceptance. For instance, most of the participants, who took part in this research chose orange-based formulations as their favourite (27). As for the doses, formulations with 50, 100, 150 and 200 mg isoleucine were created, which are acceptable for these paediatric patients (27). Moreover, formulations rapidly released the amino acid within 5 min under simulated gastrointestinal conditions (27). SSE was also used by Karavasili *et. al*, 2022 (30). The advantage of this technique is that it does not need high temperatures, and thus, it is suitable for thermosensitive APIs (30). Karavasili *et. al* (30) made cereal-dosage forms of various designs with paracetamol and ibuprofen as API. These designs and the use of colourings could improve children acceptance. Also, the use of cereal is important, as cereals are the most popular and well accepted morning breakfast meals for children (30). As for doses, Karavasili *et. al* intended to formulate cereal so that the single drug doses would be administered with one serving portion of cereal. This means that children could consume 30 g of cereal with 125 ml milk and receive 250 mg paracetamol or 100 mg ibuprofen (30). Concerning the release in the fasted state gastric conditions, in the fasted state intestinal conditions and fed state intestinal conditions with full or low-fat milk, the paracetamol cereal showed immediate release, while the ibuprofen cereal showed modified release. The ibuprofen cereal showed faster solution in intestinal conditions, due to its better solubility in alkaline media (30). Also, full-fat milk seemed to increase the ibuprofen's release, probably because the fat globules and casein micelles may encapsulate hydrophobic ibuprofen and enhanced its solubility and solubility rate (30).

Apart from SSE, there are also researches that used HME coupled with FDM, to produce chewable forms. Tabriz *et. al*, 2021 (23) and Scoutaris *et. al*, 2018 (29) are among them. Tabriz *et. al* (23) made dosage forms of diphenhydramine hydrochloride in various paediatric designs and tablet design. A great role in palatability played sucralose, as sweetener and in taste, masking the choice of HPC and gelucire suitable excipients, because diphenhydramine hydrochloride is a bitter substance (23). Of course, the palatability was enhanced by the strawberry flavouring (23). The designs along with the various colourings and the flavouring of the formulations are important for children acceptance. Moreover, the dose of 12.5 mg of diphenhydramine hydrochloride in each formulation is appropriate for children (23). Concerning the release, all formulations showed immediate release at pH 6.5, with normal tablet showing the slowest release (23). Scoutaris *et. al* (29) produced dosage forms of indomethacin with "starmix"-based designs. This is important as it could enhance pediatric patients' compliance (29). The dose of each printlet (25 mg of indomethacin), was found to be appropriate for children (29). As for the release, it seemed that at pH 7.4, the formulations showed immediate release, probably because hypromelose acetate succinate is highly soluble at pH > 6.0 (29).

Table 2: Overview of the investigated key attributes of the 3D-printed paediatric swallowing dosage forms

Swallowing dosage forms

Swallowing formulations are the most common oral dosage forms. In order to be received by paediatric patients, it is important to have suitable sizes, because children have difficulty in swallowing. The last five years, the following research groups have studied 3D paediatric swallowing forms: Malebari *et. al*, 2022 (31), Bracken *et. al*, 2022 (32), Wang *et. al*, 2021 (33), Boniatti *et. al*, 2021 (34), Cui *et. al*, 2021 (35), Krause *et. al*, 2021 (36), Januskaite *et. al*, 2020 (8), Wang *et. al*, 2020 (37), El Aita *et. al*, 2020 (38) and Palekar *et. al*, 2019 (39). Many printing techniques have been used. More specifically, HME coupled with FDM, SSE, DPE, BJP, digital light processing and selective laser sintering have been used.

HME coupled with FDM was used by Bracken *et. al*, 2022 (32), Krause *et. al*, 2021 (36), Januskaite *et. al*, 2020 (8), Wang *et. al*, 2020 (37) and Palekar *et. al*, 2019 (39). HME has the advantage of being solvent-free (37). Bracken *et. al* (32) produced tablets of three diameters (6, 8, 10 mm) without API in order to examine the acceptance by the paediatric patients. It seemed that most of them preferred the 6 mm size tablets, followed by 8 mm and 10 mm (32). In order to improve the overall cosmetic appearance of the 3D printed tablets, Bracken *et. al* (32) used titanium dioxide as opacifier. Although no flavourings were used, the use of Eudragit could help with taste masking, as it is a polymer that is insoluble at pH>5, and thus, it does not allow release in the oral cavity (32). Krause *et. al* (36) made minitablets of caffeine and propranolol hydrochloride, respectively. Minitablets were of various diameters (1.5, 2.0, 3.0, 4.0 mm), which could be easily swallowed (36). This is important for paediatric

populations, as they have problems with swallowability. As for doses, the highest dose of both APIs was in the 4.0 mm minitablets (approximately 5 mg), which is appropriate for children (36). Although there were no colourants, the different composition of minitablets had an impact on their colour. HPMC-based minitablets showed a more brownish appearance (particularly those with caffeine), while the HPC-based minitablets were more light-coloured and, especially, those with caffeine were white and those with propranolol hydrochloride had a yellowish colour (36). Concerning the release at pH 7.4, it seemed that depending on size, this could be immediate or modified (36). More specifically, the minitablets of 1.5 mm diameter showed immediate release, while those of 4.0 mm diameter showed modified release. Januskaite *et. al* (8) produced placebo printlets of the same dimensions in order to study the influence of visual appearance of the printlets prepared using different 3DP technologies on pediatric end-user visual preference. Among all printlets, the most suitable was that, which was produced by FDM (8). Due to the original colour of the PVA filament used in this study, the printlets appeared yellow in colour (8). Overall, these printlets were the least preferred (8). Wang *et. al* (37) made caffeine citrate tablets of donut shape in order to enhance the compliance of pediatric patients. The drug contents (% w/w) of the designed formulations were 5, 10, 15 or 20 %. Finally, two formulations of 15 % drug content (F6: HPC LF and HPMC K4M, F7: HPC LF, HPMC K4M and Eudragit EPO) showed appropriate printability and were tested for their dissolution rate (37). Printlets of these formulations with infill 10%, 50%, 100%, showed modified release at acidic pH. The increased dissolution rate with 10% infill density compared with the 50 and 100% infill may be attributed to the increased surface area because of the pores of the tablets (37). Although there was no use of flavouring, the composition of these formulations helped with taste masking. More specifically, Eudragit EPO, which was used in Formulation 7 is a pH-sensitive polymer that is easily dissolved at pH < 5, which masks the taste of ingredients because the polymer is insoluble in saliva and water (37). Palekar *et. al* (39) produced minicaplets of baclofen with 10% w/w drug loading. Judging from the caplets' weight, the measured doses of baclofen in each formulation were appropriate for children. The minicaplets were of 5 mm, 7.5 mm and 10 mm length and 30%, 65% and 100% infill (39). These sizes could enable better children swallowability. As for the release at the acidic pH, the 5 mm and 7.5 mm minicaplets showed immediate release, while the 10 mm minicaplets showed modified release, probably because the erosion increases in smaller minicaplets and so the dissolution rate (39).

SSE was used by El Aita *et. al*, 2020 (38) who made tablets of levetiracetam with different number of layers. Each tablet with a certain number of layers was calculated to have the desirable dose for a specific paediatric group (38). Thus, tablets with 3 layers (dose: 28mg) were for newborn infants (4kg), tablets with 5 layers (dose: 49 mg) were for infants (7 kg), tablets with 7 layers (dose: 77 mg) were for toddlers (11 kg) and tablets with 11 layers (dose: 119 mg) for preschool children (17 kg) (38). As for release at pH 6.8, all formulations showed immediate release (38).

DPE was used by Malebari *et. al*, 2022 (31) and Boniatti *et. al*, 2021 (34). Some characteristics of this method are that it does not need solvents and the produced dosage forms are less friable (31). Malebari *et. al* (31) made minitablets of lopinavir and ritonavir.

Although, the minitablets were produced by the HME technique, coupled with the FDM, it seems that the drug substance was degraded. Thus, this technique was replaced by the DPE, in which the temperature was reduced (31). The sizes of the minitablets were appropriate in order to enhance children's compliance. As for the dose, each formulation had 40 mg of API (lopinavir of ritonavir), which is appropriate for children, as the recommended doses for paediatric patients are 16 mg and 4 mg of lopinavir and ritonavir, respectively, per kg of weight (31). Concerning the release at pH 1.2 and 6.8, both minitablets of the two drug substances showed a modified release (31). More specifically, they showed faster dissolution at pH 6.8 than at pH 1.2 (31). Boniatti *et. al* (34) studied tablets with racemic praziquantel in suitable sizes for pediatric patients. Although no colourant was used, the tablets had different colours, because of the difference in their composition (34). Concerning doses, those were approximately 150 mg or 100 mg (34). As for the release at the acidic pH, all formulations showed modified release (34).

BJP or drop-on-powder (33) was used by Wang *et. al*, 2021 (33) and Cui *et. al*, 2021 (35). BJP is a simple 3D printing technique, suitable for a wide range of starting materials. Wang *et. al* (33) made levetiracetam printlets of various cartoon-based shapes using CJP. CJP is a type of BJP which combines multiple printing heads loaded with different printing inks. The colourings and shapes of those printlets could enhance paediatric patients' compliance. Moreover, spearmint flavouring, but also sucralose as sweetener, could improve the palatability of dosage forms. As for doses, printlets of four theoretical strengths were designed, which were 160 mg, 250 mg, 500 mg, 750 mg and 1000 mg. The doses are appropriate for children. The higher the dose of each printlet, the bigger its size. Concerning the release at pH 6.8, all 1000 mg printlets showed immediate release. Cui *et. al* (35) produced theophylline and metoprolol printlets of various appropriate for children diameters. The target doses for pediatric preparations were 80 mg, 160 mg and 240 mg for theophylline tablets, while for metoprolol were 2mg, 4 mg, 5 mg, 8 mg and 12 mg (35). Concerning the release in distilled water, theophylline tablets showed sustained release (97.63% in 24 h), while metoprolol tablets showed immediate release (35). Those release profiles were really close to those of commercially available formulations and with a high accuracy in dose (35). Thus, 3D printing of dosage forms with theophylline and metoprolol could be a more efficient way for adjusting the desirable dose in a formulation than other methods, such as physical tablet splitting, tablet grinding and subcontracting and tablet liquefaction, which are common, but with great inaccuracy in doses (35).

Apart from FDM and SSE (see chewable formulations section), Januskaite *et. al*, 2020 (8), two other printing techniques for producing placebo tablets, were also used. Those are the digital light processing and the selective laser sintering (8). Digital light processing is characterised by its high accuracy and superior resolution. In selective laser sintering, an extensive range of dosage forms can be fabricated. Tablets with both techniques had the same dimensions, but included different colourants. In the first technique riboflavin was used, while in the second candurin® gold sheen (8). In this study, the tablets, which were made by the digital light processing, were preferred more than the swallowing tablets (8).

Table 3: Overview of the investigated key attributes of the immediate release 3D printed paediatric orodispersable printlets and films

Orodispersible printlets

From 2017 to 2022, many researches, have studied the use of orodispersible dosage forms, as paediatric formulations. This kind of dosage forms is popular among the young patients, because it is a solution to the swallowability problem. More specific, one type of orodispersables is the printles, which are 3D printed orodispersible tablets. Díaz-Torres Eduardo *et. al,* 2021 (40) and Suarez-Gonzalez Javier *et. al,* 2021 (41) have studied orodispersible printlets of hydrochlorothiazide, as paediatric formulations. In both researches, 10 mg of hydrochlorothiazide, in each printlet, were used, as it is the paediatric dose. Moreover, the two groups used the SSE 3D printing technique. The reason for this, is that the SSE 3D printing is simple and does not reach high temperatures, which may degrade the API (40). This is important for the paediatric orodispersible printlets, as it does not have a negative impact on the therapeutic dose and thus ensuring the desirable therapeutic result. As it seems, both groups used the same excipients, which are appropriate for children. Only lactose may be related to intolerance or hypersensitivity in newborns (41). Due to the bitter taste of hydrochlorothiazide, banana flavour was used in both studies. As for the dimensions of the printlets, in the research of Díaz-Torres Eduardo *et. al*, 2021 (40) a range of dimensions in different printlets was used, while in the research of Suarez-Gonzalez Javier *et. al*, 2021 (41) a range of dimensions is not reported, *albeit* the fact that in both studies, all printlets have diameters between 4 and 5 mm. This is important for paediatric patients, because they would not face any problem, in case they swallow the formulation. Furthermore, both groups have studied the release of hydrochlorothiazide in water and found that it was immediate. This is desirable as orodispersible printlets should release the most amount of drug in oral cavity. Suarez-Gonzalez Javier *et. al,* 2021 (41) have also studied the release in HCl (0.1 N) and found a slower release than in water, which is probably due to the presence of croscarmellose sodium at the acidic pH (41).

Orodispersible films

A popular form of orodispersibles is orodispersible films. These are also forms, which are preferred by children, as they are not supposed to be swallowed. Through the last five years, Khalid *et. al,* 2021 (42), Öblom *et. al,* 2019 (44), Ehtezazi *et. al,* 2017 (43) and Wickström *et. al,* 2017 (45) have studied orodispersible films, which could be used in the therapy of paediatric patients. Khalid *et. al,* used HME, and, Ehtezazi *et. al* HME coupled with FDM 3D printing (42,43). HME has the advantage that there is no need for solvent. Although high temperatures are used in this technique, the two researchers mention minimal (42) or no degradation (43) of the APIs. Concerning the APIs, Khalid *et. al* studied diclofenac sodium, while Ehtezazi *et. al* paracetamol and ibuprofen. The doses in both studies are considered acceptable for children. In Khalid's *et. al,* work, the highest dose of

diclofenac sodium was 25.66 mg, equivalent to 25 mg diclofenac, which is the desirable dose (42). In the Ehtezazi's *et. al* work, the doses of ibuprofen are 13.9 ± 0.7, 14.5 ± 0.5 and 24.8 ± 1.6 mg, while the doses of paracetamol are 27.1 ± 1.2, 15.1 ± 0.4, 24.5 ± 0.3 and 8.5 ± 0.3 mg, which are safe for the paediatric population (43). Moreover, in the two studies different excipients have been used to achieve the desirable formulations with suitable release. Both used flavourings. *Khalid, et. al* used mint and licorice mint flavours and Ehtezazi *et. al* used freeze-dried strawberry powder, in order to reach patients acceptability and compliance (42,43). Khalid *et. al* also used TiO_2, as colourant to make films appearance completely homogenous and whitish (42). Both studies chose square shape formulations, but Khalid *et. al* produced also rectangles and Ehtezazi *et. al* circles (42,43). In Khalid's *et. al,* work it seems that for the same formulation, film of bigger area includes more drug substance, which is useful for personalised films (42). As for the release, formulations of both Khalid *et. al* and Ehtezazi *et. al* showed immediate release. In *Khalid's, et. al* report the dissolution media was deionised water and pH 5.7 simulated saliva fluid and in both media the release of all formulations was 80% in approximately 3 minutes (42). This is important, as the goal of orodispersibles is to release the highest amount of drug in the oral cavity.

The other two research groups used inkjet printing, but Öblom *et. al* also used the SSE printing (44,45). Öblom *et. al* employed two different techniques in order to compare them in the production of orodispersible films of warfarin sodium (44). Judging from the doses, which were 0.1, 0.5, 1 and 2, the films developed by Öblom *et. al* are suitable for paediatric patients. In Wickström's *et. al* work, the APIs were the vitamins B1, B2, B3 and B6 and the doses of all the vitamins in the films were suitable for children (45). In the two studies, different excipients were used (44,45). In detail, Wickström *et. al* used rice paper (made of potato starch, vegetable oil, and water) and sugar paper (containing starches (E1422, E1412) maltodextrin, glycerine, sugar, water, stabilizers (E141, E471), food colour (E171), citric acid, flavours, preservative (E202), sucralose). In both cases, in the inkjet printing, the ink was yellow. More in particular, *Wickström, et. al*, used an edible yellow ink that was comprised of water, glycerol, tartrazine (1.5%), propylene glycol, and citric acid. Colourant is important in paediatric formulation as it makes the films more appealing to children. Both studies chose square shape for their films. Öblom's *et. al* reported that the films of bigger area, including more drug substance, are more useful for personalised forms (44). As for the release, Öblom *et. al*, found that immediate release in purified water was achieved for all formulations. More specifically, all dosage forms with a target dose of 2 mg (the highest dose) released 80% of the drug within the first 30 min and both SSE films and inkjet printing films displayed a similar drug release behaviour (44). This is desirable for films, because they must release the highest possible quantity of the drug substance in the oral cavity.

4. Conclusions

In order to transite from mass production to individualised pharmacotherapy, the pharmaceutical industry is becoming more and more interested in the new 3D printing manufacturing technology. The aim of this review was to collect all the currently available

research reports that relate to 3D printlets for paediatric patients and especially the excipients used to produce various colours, flavours, shapes and sizes. 3D printlets for paediatric population can be divided into three main categories; the chewable dosage forms that include the solid forms, and the soft forms or gummies, the swallowing dosage forms, that are small in size to aid the swallowability, and the orodispersable dosage forms that can be either printlets or in the form of films. Regarding the chewable formulations researchers have tested many colours, flavours, shapes and dimensions. Scientists used mainly pectin and gelatin to produce the so called gummies. Another approach was the manufacture of paediatric SSE 3D printed oral dosage forms based on chocolate and cereals. In some cases the produced formulations have been tested in clinical trials, showing better results than the commercially available tablets as caregivers mentioned that the flavoured printlets were more acceptable by the children. Concerning the swallowing dosage forms many methods and excipients were used to produce printlets with various colours, flavours, shapes and small sizes (minitablets or minicaplets). In relation to orodispersables, the research for paediatric formulations was narrower. Flavours used were fruity and minty, colours were opaque and yellow, while the shapes were limited to square, triangle and circle.

Thus, the advantage of 3D printing manufacture of paediatric formulations is that the younger patients are benefited from the flavour, colour, shape and size of the printed formulation, according to their preferences. It is noteworthy that due to the ability to choose the characteristics of the youngsters' medicines, through the software, the systematic intake of the printlets increases the effectiveness of their treatment.

Concluding, this review provides an overview of the recent developments in excipients utilized in 3D printed formulations for paediatric use over the past five years (2017-2022) in order to assist formulation scientists in choosing the best excipients for product manufacture. Both patients and the pharmaceutical industry may benefit as new formulations can be brought to market faster.

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Table 1: Overview of the investigated key attributes of the immediate released 3D printed paediatric chewable formulations (solid dosage forms and soft dosage forms/gummies)

Dosage form/ release rate*	Printing method	API(s)	Excipients	Flavours	Colours	Shapes	Dimensions (mm)	Ref.
solid *(immediate)*	SSE	propranolol	gelatine, carrageenan, CMS-Na, glycerine, maltitol, sucralose, citric acid, gaba, ferulic acid	orange	carmine	capsule, diamond, flower, bear	-	(19)
soft *(immediate)*	SSE	paracetamol	mycusini® 3D choco dark	dark chocolate	-	cube	L x W x H: 8 × 8 × 5 to 22 × 22 × 17	(20)
solid *(immediate and modified)*	SSE	ibuprofen	soluplus, PVP VA-64, eudragit EPO	-	-	tablet	D x H: 10 x 3 or 2.4	(21)
soft *(immediate)*	SSE	lamotrigine	gelatin, SE600 reduced starch syrup, HPMC	-	monascus pigment, red beet pigment, spirulina algae, gardenia, purple sweet potato, grain of gramineous plants, bamboo charcoal	square, star, diamond, pentagon, heart, cylinder, triangular, hemisphere, doughnut	L x W x H: 10 x 10 x 3 (square)	(22)
soft *(immediate)*	HME/ FDM	diphenhydramine HCl	sucralose, gelucire 48/16TM (GLC), hydroxypropyl cellulose	strawberry	food grade colourings yellow, green, blue, red	smurf, palm, cherry, banana, tablet	-	(23)
soft *(immediate)*	SSE	isoniazid	corn starch	-	blue food colouring	tablet, cube, heart, moon, dog	D x H: 11.3 x 6.5	(24)
solid (in SGF pH 2.0: *paracetamol: immediate IBU: modified)*	SSE	paracetamol, ibuprofen	bitter chocolate, corn syrup	chocolate	-	star, cartoon characters	L x W x H between: 59.1X33.1X3 to 61.8 X 84.1 X 6	(25)
soft	SSE	-	sucrose, pectin, maltodextrin	lemon	yellow	cylinder/disk	D x H: 10 x 3.6	(8)
soft *(personalised release: immediate or modified)*	SSE	ranitidine hydrochloride	corn starch, carrageenan, xanthan gum, gelatine, liquid sweetener (Edulcorante de mesa líquido, Hacendado), purified	strawberry	food grade colouring (Colorante alimentario Vahiné®, McCormik España S.A.)	disk, heart, gummy bear	L x W x H: disk: 15.01 x 15.00 x 4.27 heart: 19.59 x 16.45 x 2.94 gummy-bear (80% infill): 20.56 x	(26)

			water				10.97 x 7.44 gummy-bear (65% infill): 20.44 x 10.98 x 7.42	
soft *(immediate)*	SSE	isoleucine	sucrose, pectin, maltodextrin	strawberry, orange, lemon, raspberry, banana, coconut	red, orange, yellow, light blue, light green, black	cylindrical	D x H 8.2 ×4.1 10.8 ×5.4 12.5× 6.25 13.9 × 6.95	(27)
soft *(modified)*	SSE e-3DP	ibuprofen paracetamol	gelatin glycerol EP locust bean gum (from ceratonia siliqia seeds)	-	brilliant blue, lake allura red	lego™brick	W x L x H: 20 x 29.52 x 0.45	(28)
soft *(immediate)*	HME/ FDM	indomethacin	PEG, hypromelose acetate succinate	-	-	starmix®	-	(29)
solid *(paracetamol: immediate IBU: modified)*	SSE	paracetamol ibuprofen	cereal, high purity water		red and yellow food colouring	alphabet letters, star, heart, torus, flower, mesh	-	(30)

* Release rate as stated by the author(s), CMS-Na: sodium carboxymethyl starch, D: diameter, e-3DP: embedded 3D Printing, EPO: Eudragit EPO, FDM: fused deposition modelling, gaba: *γ*-aminobutiric acid, GLC: gelucire 48/16TM, H: height, HME: hot melt extrusion, IBU: ibuprofen, L: length, MCC: microcrystalline cellulose, PEG: polyethylene glycol, PVP: polyvinylpyrrolidone, SGF: simulated gastric fluid, SOL: soluplus, SSE: semi-solid extrusion, SSF: simulated saliva fluid, W: width

Table 2: Overview of the investigated key attributes of the 3D-printed paediatric swallowing dosage forms

Dosage form/ release rate*	Printing method	API(s)	Excipient(s)	Colours	Shapes	Dimensions (mm)	Ref
minitablets *(modified)*	DPE 3DP HME / FDM	lopinavir ritonavir	PEG 4000 magnesium stearate hypromellose acetate succinate	-	spherical	D: ritonavir: 6.3 lopinavir: 6.6	(31)
tablets	HME / FDM	-	eudragit EPO, sodium phosphate fumarate, talc, triethyl citrate FCC	TiO_2	round	D: 6, 8, 10	(32)
tablets *(immediate)*	BJP/CJP	levetiracetam	MCC, mannitol, sucralose, colloidal silicon dioxide, polyvinylpyrrolidon, glycerine, polysorbate 20	food grade water-soluble pigments	carton (e.g. rabbit, bear, heart, candy)	D x H: 18.5 x 8.33	(33)
tablets *(modified)*	HME / DPE	racemic praziquantel	kollidon® VA 64, kolliphor® SLS Fine, span™20	-	cylinderl	D x H: P 50: 9.720 x 3.579 M 50: 9.810 x 3.554 M 35 span: 9.982 x 3.507 M 35 SLS: 9.841 x 3.591	(34)
tablets *(theophylline: sustained metoprolol: immediate)*	BJP	theophylline metoprolol	hydroxypropyl cellulose, MCC, lactose, polyvinyl pyrrolidone, croscarmellose sodium, polyoxyethylene (WSR N750)	-	cylinder of various volumes	D: TP tablets: 11.2 - 16.3 MT tablets: 7.2 - 9.0	(35)
minitablets *(immediate or modified release in pH 7.4 depending on diameter)*	HME / FDM	caffeine propranolol HCl	Hypromellose, Hyprolose, PEG 6000, fumed silica	(-	cylinder	D x H: 4.0 x 3.0 3.0 x 2.0 2.0 x 1.5 1.5 x 1.0	(36)
tablets	DLP	-	bis (2,4,6-trimethylbenzoyl)phenylphosphineoxid, PEGDA	riboflavin	cylinder /disk	D x H: 10 x 3.6	(8)
	SLS		PVA-PEG	candurin® gold sheen			
	FDM		PVA filament	-			
tablets *(formulations F6,F7 with infill 10%, 50%, 100%: modified)*	HME / FDM	caffeine citrate	HPC LF HPC HF HPMC K4M eudragit EPO	-	donut	D: 10 H: 5 R: 3.5 tube T: 3 wall T: 0.2	(37)
tablets	SSE	levetirace	PVA-PEG	-	round	T x D:	(3

(immediate)		tam				3 layers: 0.862 x 9.797 5 layers: 1.442 x 9.754 8 layers: 2.286 x 9.746 11 layers: 3.147 x 9.760	8)
minicaplets *(L=5 and 7.5: immediate* *L=10 gradual)*	HME / FDM	baclofen	PVA sorbitol	-	caplet	L: 5, 7.5, 10	(39)

* Release rate as stated by the author(s), BJP: binder jet printing, CJP: colour jet printing, D : diameter, DLP: digital light processing, DPE: direct powder extrusion, FDM: fused deposition modelling, H: height, HME: hot melt extrusion, HPC: hydroxypropylcellulose, HPMC: hydroxypropyl methylcellulose, IBU: ibuprofen, L: length, MCC: microcrystalline cellulose, MT: metoprolol, PEG: polyethylene glycol, PEGDA: polyethylene glycol diacrylate, PVA: polyvinyl alcohol, R: radius, SLS: selective laser sintering, SLS: sodium laurilsulfate, SSE: semi-solid extrusion, TP: theophylline, W: width

Table 3: Overview of the investigated key attributes of the immediate release 3D printed paediatric orodispersable printlets and films

Dosage form	Printing method	API(s)	Excipient(s)	Flavour(s)	Colour(s)	Shape(s)	Dimensions (mm)	Ref
printlets	SSE	hydrochlorothiazide	polyvinylpyrrolidone, CCS, lactose monohydrate	banana	-	cylinder	D x T: 4.39-4.94 x 1.40-1.73	(40)
							D x T: 4.62 x 1.62	(41)
films	HME	diclofenac sodium	maltodextrin, glycerol, sucralose	mint, licorice mint	TiO_2	square, rectangle	W x L: 10x10, 10x20 20x30, 20x100	(42)
	HME/ FDM	paracetamol, ibuprofen	PVA, PEO, starch, sodium starch glycolate CCS, SLS	strawberry	-	circle, square	circular (D x T): 20 x 0.2 square (LxWxH): 20 x 20 x 0.2	(43)
	SSE IJP	warfarin sodium	hydroxypropylcellulose (SSE) propylene glycol (IJP)	-	quinoline yellow (IJP)	square	W x L: <u>for 0.1 mg</u>: 5 x 5(SSE) 4.4 x4.4 (IJP) <u>for 0.5 mg</u>: 11.2x 11.2 (SSE) 9.8x9.8 (IJP) <u>for 1 mg</u>: 15.8 x 15.8 (SSE) 13.9 x 13.9 (IJP) <u>for 2 mg</u>: 22.4 x 22.4 (SSE) 19.7 x 19.7 (IJP)	(44)
	IJP	vitamins B1, B2, B3, B6	rice and sugar paper	-	tartrazine	square	-	(45)

CCS: croscarmellose sodium, D: diameter, FDM: fused deposition modelling, H: height, HME: hot melt extrusion, IJP: inkjet printing, L: length, PEO: polyethylene oxide, PVA: polyvinyl alcohol, SLS: sodium lauryl sulphate, SSE: semi-solid extrusion, T: thickness, W: width

Figure 1: Examples of chewable formulations

Figure 2: Examples of flavours used in 3D printlets

Figure 1

Figure 2