Assessment of selective laser sintering (SLS) 3D printing as a manufacturing technique for pediatric dosage forms

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Table of contents:

Layman's Summary

Three-dimensional (3D) manufacturing technologies for patient-centric drug development unfortunately has not been extensively utilized in pediatric populations. With the pediatric population representing a small segment of sick people in the world, little investment is given as a result of lower demand in comparison to other segments of the population. Being highly heterogeneous due to non-linear development from a pharmacokinetic perspective as well as specific sensory preferences in medications parents and care givers are forced to administer off-label or simply medications with unsuitable dosages to their children, exposing the kids to various health risks. In order to meet various criteria needed for pediatric dosage forms a powder based 3D printed manufacturing method called Selective Laser Sintering is utilized (SLS). SLS is investigated as a manufacturing method because it is one that can use thermoplastic and pharmaceutical grade polymers to manufacture the dosage forms. Having a wide range of modifiable printing parameters as well as a large selection of polymer materials, SLS offers great manufacturing flexibility needed to meet the pharmaceutical needs of pediatric populations.

Though literature review it has been established that younger children show preference and acceptability towards minitablets (2-3 mm diameter) as well as oro-dispersible tablets, which are tablets that undergo rapid disintegration and drug release upon contact with water or saliva. These dosage forms are seen as the most important for younger pediatric populations as they present little to no swallowing difficulties and can be modified in terms of dosage. The reported findings demonstrate that manufacturing of oro-dispersible tablets is possible by choosing a polymer material of spherical morphology and particle size within defined ranges. This allows for formation of a porous polymer matrix as long as it is done at a relatively high printing speed. Porosity is regarded as the most important factor as it allows for incorporation of various taste-masking substances as well as allowing for rapid disintegration of the tablets.

By using lower printing speeds, it is also possible to manufacture minitablets that illustrate great dosing flexibility as by using different polymers, incorporated drugs can be released at different rates, thus allowing for adjustability of drug dosages for children. Reduced frequency of drug intake can also be achieved by mixing different polymer/drug formulations in the printer, and

since printing is done layer by layer this allows for manufacturing of 1 minitablet, containing 2 different drugs that are released at different rates.

In addition to this the ability of SLS to manufacture complex shapes and geometries with modified drug release properties is shown for tablet dosage forms aimed at adolescent population segments.

Overall SLS can be considered a suitable method for manufacturing of dosage forms for pediatric populations due to its ability to meet various pediatric needs from the standpoint of masking unfavored tastes of medications as well as being able to precisely adjust dosages in medications while minimizing the frequency of taking medications, facilitating pediatric adherence.

Abstract

Heterogeneity of the pediatric population means that several different requirements must be met in order to provide the pediatric population with medication suited to their needs. Due to different rates of development in terms of pharmacokinetics as well as motor skills children require tailored dosage forms where the dose of the active pharmacological ingredient (API) can be modified to their needs and the size of the medication is acceptable in order to avoid choking on the medications. In order to make sure that the child obtains the intended dose it is crucial that the developed dosage forms are palatable, ensuring adherence to the treatment. Selective Laser Sintering (SLS) has been employed as an additive manufacturing method capable of utilizing several thermoplastic and pharmaceutical grade polymer powders while providing flexibility in the manufacturing process due to its variable parameters as well as the ability to manufacture complex structures. Key parameters associated with dosage form manufacturing have to do with the energy density applied to the formulation powder which allows particles to undergo a sintering process where they are fused together though bridge formation without fully fusing together in a melt. Concerning energy density, Laser scanning speed (LSS), heating temperature and scan spacing have been identified as parameters with the most significant effect on the composition of the matrix. Oro-dispersible tablets (ODTs) as well as mini tablets have been chosen as key dosage forms for younger segments of the pediatric population as they present no swallowing difficulties.

Vinylpyrrolidone-vinyl acetate copolymer (KVA64) was shown to be an optimal polymer for formation of ODTs. With favorable thermal properties such as Tg of ~100C as well as optimal spherical morphology and a relatively low particle size, at high LSS KVA64 was shown to be able to establish highly porous matrices that allowed for incorporation of various taste masking excipients as well as shielding of thermosensitive API by lowering printing temperature via plasticization.

In order to manufacture minitablets, the laser scanning speed had to be lowered significantly and more coarse polymers were incorporated, allowing for denser formulations with reduced porosity. Drug release profiles were also tailored though utilization of Ethyl cellulose (EC) and poly (vinyl alcohol)–poly(ethylene glycol) graft copolymer (KIR) which due to their different chemical properties as well as size and morphology allow for sustained and instant release of API

respectively. Incorporation of dual APIs was also demonstrated via matrix manipulation possible due to SLS's layer by layer manufacturing.

Manipulation of release profiles has also been shown for standard tablet formulations (10 mm) where altering the shape and the polymeric material by giving it more surface area as well modifying its internal structure to be more porous as in the case of a 95% pure Paracetamol dosage form allows for tailored drug release profiles.

1. Introduction

Since as early as 2012 the application of Three-dimensional (3D) printing technologies has been expanding and is becoming more adopted into the field of pharmaceutics. The unique advantages of 3D printing allow researchers to focus on patient-centric drug development and new drug formulations [1]. However same cannot be stated for drug formulations in the field of pediatric medicine. The pediatric population represents a small population of all sick people in the world [2]. And whilst that may seem like beneficial statistic, being a small group also means that there is less attention and demand as well as a smaller market segment, with companies unwilling to invest in expensive trials in a limited market [3]. Additionally, unlike adults, the pediatric population aged 0-17 years old, is a highly heterogenous population group that requires specific parameters to be met in drug formulation based on multiple factors [2].

The first reason for such high variability in the pediatric population stems from the fact that children's development is non-linear and progresses at a different rate for each subset of the population. From a pharmacokinetic perspective, for oral administration of drugs alone there are various age-dependent changes that occur in the gastrointestinal (GI) tract that affect the way drug substances are absorbed, distributed, metabolized and excreted [4]. For example, stability and ionization of a drug is highly dependent on the pH in the GI tract. In the neonatal period of development, the intragastric pH levels are elevated, meaning that drugs of various of degrees of acidity must be carefully tailored in terms of dosage. Weak acids will result in limited bioavailability if given in the same dosage as a strong acid drug such as penicillin [5]. Other developmental factors that affect the pharmacokinetic nature of the drugs are biliary function, gastric emptying as well as the maturity of organs and organ systems [5]. A linear dose-weight correlation applied for adult dosing most of the times does not work with children due to the above-described factors.

Additional issues arise when it comes to drug adherence in the pediatric population. Preference towards different drug formulations may seem trivial, but from a pediatrician's perspective having a palatable formulation of an appropriate size can be a crucial factor in treatment of a child [4]. Although little evidence exists on the correlation of poor taste and decreased adherence to the medication, palatability, as cited as by researchers and parents is an important factor when it comes

to medicine adherence [6]. With many parents and pediatricians struggling to force ill children to take medication that they dislike, resulting in spitting and/or vomiting of the medication and subsequently the child not receiving an appropriate therapeutic dose. Texture and smell are cited as additional significant factors however taste ranks at the top [6].

When it comes to size of the dosage forms, children develop their cognitive and motor skills at different rates and their ability to swallow medications varies greatly [4,7]. Eliminating unnecessary discomfort associated with taking medications is key to adherence of treatment, and provision of appropriate dosage forms is necessary to avoid death due to choking or inappropriate pharmaceutical dosing.

With a large number of medications not being tailored to the needs of pediatric patients and the development of pediatric dosage forms being hindered by high developmental costs and ethical considerations regarding clinical trials and with even authorized medications for the neonatal population not being age appropriate in regard to the dosage forms, pediatricians often resort to off-label medication usage [4] with 1/10 medications prescribed to children being off-label [8].

Unavailability of suitable dosage forms leads parents and professionals to manipulate the dosage to attempt to make it more suitable for the children. When it comes to solid oral dosage forms this includes tablet splitting and crushing [4]. Administration of dosage forms in such a manner is poor practice as not only can it expose a household to the drug, but it is also unknown what effect this has on the stability, bioavailability and pharmacokinetics and dynamics of the drug [4]. For example, a study of pharmacokinetics of Lopinavir/Ritonavir (antiretroviral medication) in a crushed versus solid form revealed that administration of crushed form of the medicine reduced the AUC by approximately 40%, which in the case of a retroviral medication is a big issue [9].

Due to the described limitations a change in the way pediatric formulations are approached is essential. Caregivers need to have the ability to provide flexible dosage forms with acceptable palatability that are safe and easy to administer. This is where 3D printing technology can be a major step in disruption of the paradigm in the pediatric formulation sector.

3D manufacturing has the potential to be the technology that moves the pharmaceutical industry away from mass production of generalized formulation forms towards personalized customizable formulations. 3D printing or additive manufacturing, is an umbrella term that incorporates various printing techniques with their unique characteristics and advantages. The American Society for Testing and Materials (ASTM) classifies additive manufacturing processing into 7 different categories [10], out of which powder bed fusion is the primary focus of current research. Powder bed fusion remains one of the less investigated manufacturing methods in the field of pharmaceutics, whilst also having favorable aspects such as good resolution and powder as a feedstock material, being very similar to major pharmaceutical manufacturing processes [11]. Within powder bed fusion there are 4 different technologies, namely Selective Laser Sintering (SLS), MultiJet Fusion (MJF), Selective Laser Melting (SLM) and Electron beam Melting (EBM) with the main difference between the four being the materials utilized as well as the form and density of light used to transmit thermal energy onto the powder bed [12]. Considering the fact that SLM, EBM and MJF deal with metals or alloys and in the case of MJF it exclusively utilizes Nylon, SLS is the most suitable candidate as it allows for manufacturing of formulations using various thermoplastic and pharmaceutical grade powders [13].

As it was established earlier in order to manufacture suitable pediatric dosage forms a great deal of flexibility is required. It is hypothesized that using a 3D printing approach such as SLS, due to its variability in processing as well as the diversity of polymer substrates that can be used for pediatric dosage formulations, precise requirements in terms of dosage, color, shape and size can be met, thus alleviating the stress of using off-label formulations or inaccurate self-dosing due to unavailability. SLS can offer quick personalization of medicine and is also associated with relatively small costs for individual small batches production in comparison to conventional mass-production manufacturing techniques [14,15].

Therefore, the goal of this literature review is to analyze whether SLS can be used for manufacturing of pediatric dosage forms.

2. Selective Laser Sintering (SLS)

As previously mentioned SLS is a subset of a powder bed fusion additive manufacturing method. Originally developed by Carl Deckard in 1984, SLS used to utilize a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser with a power output of 100 Watts (W) [13]. Today however most commercially available printers either use diode or a Carbon dioxide (CO_2) laser due to their low cost and high-power output. Diode lasers, depending on the semiconductor material used to direct the wavelength of the laser beam can range from the IR to UV-Vis spectrum. However, since most of pharmaceutical grade polymers are white or transparent, the absorption of diode lasers being in the visible light spectrum, results in minimal absorption with little to no powder fusion of powder particles, thus requiring an absorption enhancer [13]. CO_2 lasers on the other hand having the laser wavelength of 10.6 μm [16] in comparison to that of commercially available diode printers having the wavelength of 445 [17], 450 [13] and 808 nm [18] are a good candidate for sintering of thermoplastic polymers due to high absorption achieved due to higher laser wavelength.

Figure 1 illustrates a schematic representation of a commercially available SLS 3D manufacturing unit. Operation of the SLS unit begins with programming and digital rendering using computer aided design (CAD) software. Following the design of the to be printed object, it is converted to a machine readable STL file which describes an external surface of the 3D object [19].This file is exported and sliced into distinct cross-sectional layers using the 3D printer's programs [15,19,20]. The chosen feedstock powder is loaded into the powder supply chamber, spread over the building platform and is levelled using a roller similar to the one illustrated in in *Figure 1* [20]. A blade can also be used as a tool for spreading of the powder. Prior to printing of the designed object, the powder bed is gradually heated from room temperature to the programmed temperature and is continuously heated throughout the manufacturing process [20]. The build platform is moved down by one layer thickness, and a fresh layer of powder is rolled out from the supply chamber. Next, following the cross-sectional data from the STL file a laser unit directs a beam to a galvo mirror and traces the cross-section on the powder-bed in accordance with the designed geometry. The polymer particles in the selected regions are then heated below their melting/ glass transition temperatures and are fused together though bridge formation without the liquification of the powder (sintering) [20,21].

The axis pistons move the supply chamber up and the build chamber down while the roller moves across the building platform, distributing the next layer of powder. This process is repeated layer by layer until the 3D object is completed.

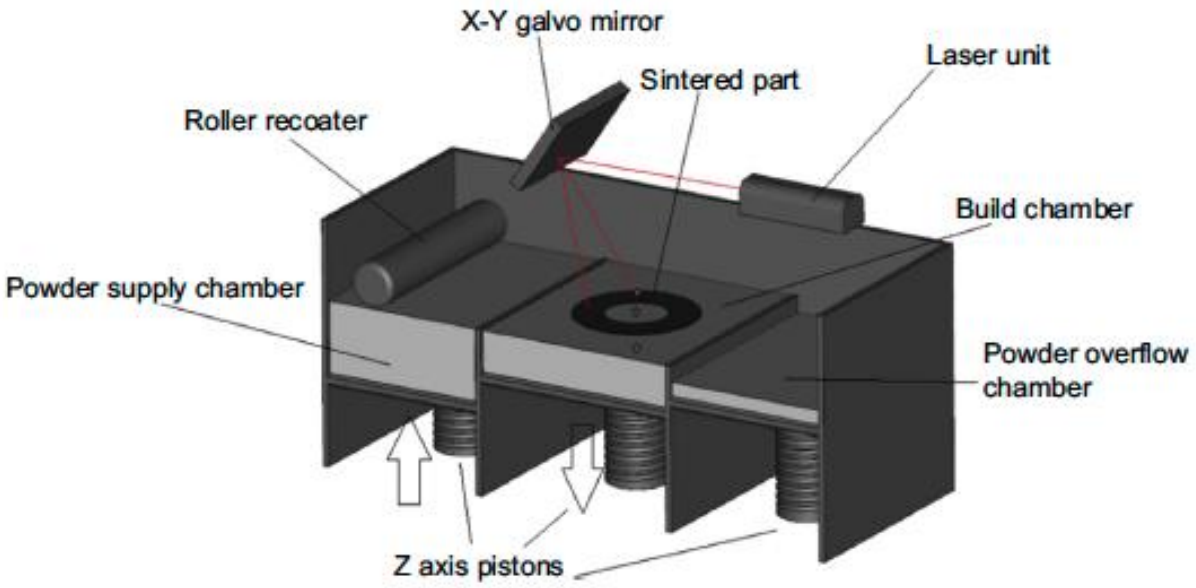

Figure 1: Schematic representation of SLS printing set-up [20].

Due to the presence of loose powder particles and the precise laser directing, SLS can manufacture intricate overhanging structures since the loose powder provides supplementary support to the structure formation [13]. As well as allowing for fabrication of complex geometries without the need for additional support materials this advantage of SLS manufacturing can enhance productivity as parts can be stacked in the powder bed, increasing the number of parts that can be produced per build and thus being a cost saving technique [13].

After the manufacturing is complete the powder bed is allowed to cool prior to the removal of the printed object from the build chamber. The un-sintered polymer powder can be reused to a degree, depending on the polymer material selected [20].

The high degree of flexibility in manufacturing using SLS stems from the fact that there are several printing parameters that can be manipulated independently or in combination and will yield in

different structural and mechanical properties of the printed object. Additionally, the fact that SLS can print using several thermoplastic polymer materials influences the way these parameters have to be adjusted and dictates which materials should be selected depending on the intended application. A summary of these parameters can be found in *Table 1* as well as the potential impacts they have on the selected materials and vice versa.

Table 1: Variable printing parameters and their influence on selection of polymeric materials and the properties of manufactured objects

Printing parameter	**Description**	**Effect on the polymer material**
Print temperature	Print temperature (°C) is defined by: 1) Powder bed temperature, which is the temperature of the powder in the platform [13,16]. 2) Chamber temperature which is the ambient temperature inside in the printing chamber [13,16].	Printing temperatures are unique to each material. For amorphous polymers bed temperature must be set to or slightly above the glass transition temperature (T_g) [22]. At T_g the molecular chains of amorphous polymers are in loosened motion, allowing for the consolidation of the polymer [22]. For crystalline polymers, for a similar reason the temperature must be set 3-4°C below melting point (T_m) [23]. For Semi-crystalline polymers or mixtures of 2 different polymers the temperature must be set as close to their T_g. as possible [13].
Laser power	Power of the laser, measured in Watt (W) is the optical output induced on the powder bed surface as the laser scans the area [16].	The same laser power cannot be applied for particles of different morphologies. For loose powders with finer sizes the polymer matrix will be porous, and the laser will penetrate deeper into the matrix thus enhancing absorption. If too much absorption by the powder bed occurs, the material can melt or degrade [13].
Laser Wavelength	Laser wavelength (λ) has a significant impact on the absorbance of the polymer material. Wavelength of the laser is an unmodifiable parameter however the absorptance of the material can be modified by manipulating laser power and scanning speed [13].	Selected polymer materials must be able to absorb the wavelength of the laser beam otherwise it will not undergo sintering. Pharmaceutical grade colorants can be added to enhance absorptance [13].
Scanning speed	Scanning speed (mm/s) is the rate of movement of the laser beam as it travels across the powder bed. Slower scanning speed result in a higher energy output of the laser due to increased contact time with the powder bed and vice versa [13,22].	Printing at higher scanning speeds allows for formation of more porous polymer matrices due to a reduced energy density and hence minimal bridge formation between particles [13].
Scan spacing	Scan spacing is the difference between two consecutive scanning vectors [16]. Scan spacing should not be bigger than the diameter of the laser beam. If it is the sintering cross section will be incomplete [23]. Scan spacing and printing time are proportional parameters.	Decreasing scan spacing reduces printing time which will result in thinner and more intricate structures. However, if scan spacing is too short in proportion to the laser beam diameter it can induce thermal deformations [13].
Layer thickness	Layer thickness (μm) is the height of each individual layer. Layer thickness has an inversely proportional relationship to printing time. Smaller layer thickness increases printing resolution and the less rough the surface is [23].	Layer thickness is dependent on the penetration depth of the polymer used (degree to which the energy can penetrate the matrix of the material. Outside of printing parameters influencing the energy density of the laser this largely depends on particle size, powder density [23].

3. Pediatric requirements for consideration when printing with SLS

Conventional dosage forms such as tablets and capsules are not always suitable for younger children due to issues associated with swallowing. A study by Ranmal et al., has found that children aged 6-11 years old have a high preference for mini-tablet (2-3 mm) and oro-dispersible dosage forms (ODTs) [24] in comparison to regular sized tablets (10 mm) as well as capsules. There have also been studies that evaluated the ability of children aged 2-3 years old [25] as well as 6 months – 5 years old [26] to swallow 2-3 mm uncoated tablets. The reported findings indicate the ability of children to swallow minitablets as well as showing a preference in acceptability and palatability of minitablets in comparison to 3mL syrup dosage form. Due to the acceptability of mini-tablets as dosage forms in the younger segment of the pediatric population, they, as well as oro-dispersible dosage forms that do not need to be swallowed, are considered to be key dosage forms for younger segments of the pediatric population. For the adolescent group of the pediatric population (12-17 years old) [24] ODTs and mini tablets can also be utilized when swallowing difficulties are present, however with age, a preference towards the more "adult" dosage forms such as tablets and capsules (10 mm in diameter) is shown, with adolescents a 1 tablet over multiple small tablets attitude is seen [24]. For this reason, tablets are also investigated as a SLS printable dosage form for that age group.

In other to be suitable for pediatric use, the selected dosage forms need to contain an amount of the active pharmaceutical ingredient (API) adjustable to the age and the needs of the child [27,28]. It is crucial to account for the change in the magnitude of dosage since as previously mentioned, children undergo non-linear development in terms of organ maturity and metabolism [4]. Palatability in terms of taste, smell, size and texture is another important criterion that must be considered [27]. Since palatability has a strong effect on compliance, dosage formulations containing unpalatable API's will require taste masking [27,29]. Due to high variability in children's pallets when it comes to preferred tastes the primary objective for manufacturing of dosage forms with poorly palatable API's should be taste masking with the aim of achieving a neutral flavor or at least to reduce the unpleasant characteristics of the API. For other sensory parameters taste, texture and size are considered as most impactful factors for acceptability of dosage forms [7,24,27], with color considered as the least important [24]. The final factors to be considered from a pediatric perspective are minimal dosing frequency in order to simplify

compliance, minimal number of excipients and compatibility of the dosage form with elevated acidic conditions due the increased pH in the GI tract during infancy [27,28].

4. Solid oral dosage form characteristics for SLS manufacturing

The polymer feedstock materials must meet certain criteria in order to be optimal for SLS manufacturing. In general polymers with low T_g and T_m should be chosen as otherwise the printing temperature has to be elevated in order to consolidate the polymers, increasing the risk of thermal degradation of the API as well as other excipients. Thermal properties of excipients must also be considered as excipients with T_g or T_m lower than the main polymeric carrier may result in excess sintering due to the thermal pool formation and if higher, the polymer will undergo sintering to a much smaller extent and will require additional energy density to be applied in order to be consolidated, impacting the structure and the mechanical properties of the dosage form.
The used polymer must also be able to absorb at the wavelength of the laser used, this is possible in printing with a CO_2 laser as thermoplastic polymers absorb at its wavelength [11], for a diode laser however an absorbance enhancer would need to be incorporated into the formulation.

Morphology and size of the particles is another factor crucial in successful manufacturing of dosage forms. According to studies by Gueche et al., and Madžarevic et al., the preferred morphology for SLS manufacturing is spherical particles having the recommended particle size range of 45-90 μm [30] and 58-180 μm [31]. Using particle sizes within these ranges should prevent selection of coarse particles with poor packing density associated with broad particle size distribution and particles that are too fine and can result in agglomeration, hindering the manufacturing process. Hausner ratio (HR) is a good measure for flowability, based on bulk density (BD) and tapped density (TD) (HR= TD/BD) with lower values (~1) serving as indicators of good flowability [30].

In addition to the above-mentioned factors the manufactured dosage forms need to have sufficient harness (N), allowing for handling without disintegration. Additionally, in order to be considered as ODTs, the manufactures dosage forms must disintegrate within 30 seconds according to the FDA [32] and 3 minutes according to European pharmacopeia [33].

5. Oro-dispersible tablets (ODTs)

SLS is well suited for manufacturing of ODTs. As there is no need to compress the dosage forms as well as its ability to loosely bind powder particles, the dosage forms obtained from SLS can be very porous. Porous matrices of ODTs, once exposed to a medium allow for fluid penetration into the open pores (pores exposed to the surface), resulting in accelerated breakdown of the dosage form without the need to swallow it whole.

Several studies have investigated the ability of SLS to manufacture ODTs. Vinylpyrrolidone-vinyl acetate copolymer (Kollidon VA 64 also known as Copovidone) further abbreviated as KVA64, is usually the polymer of choice when it comes to ODTs. One of the first ODT manufacturing studies via SLS by Fina et al., investigated both KVA64 (T_g = ~100°C) [34,35] as well as hydroxypropyl methylcellulose (HPMC) (T_g = ~162°C) [36] as polymer carriers making up for 92% of the ODT with Paracetamol in a 5% API loading [37]. Using a 445nm 2.3W blue diode laser equipped SLS printer (Sintratec Kit, AG, Brugg, Switzerland) 3 different laser scanning speeds (LSS) were investigated with the objective of making ODTs with fast release properties. With chamber and surface temperatures for HPMC and KVA64 being 115,135°C and 80, 100°C respectively, by altering the LSS from 100 – 300 mm/s, an increase in total porosity (sum of open and closed porosity percentages) for both polymers was observed, with an increase from ~ 16.5 to 34.6% for HPMC and ~20 to 40% for KVA64. Breaking force values will not be reported in this section of the literature review. As there are no breaking force requirements for ODTs, unless they break during handling, they are deemed acceptable for use. Disintegration of the ODTs measured in water found that HPMC dosage forms manufactured at 100,200 and 300 mm/s as well as KVA64 manufactured at 100 mm/s disintegrated in >600s while KVA64 manufactured at 200 and 300mm/s disintegrated at 320 and 4 s respectively [37]. Fina et al., does not provide an explanation for such stark differences in the disintegration of both polymers. It is possible that KVA64, as a significantly bulkier structure due to its aromatic regions has a greater distance between its polymer chains in comparison to HPMC and therefore allows for easier medium penetration due to a less tight matrix.

The LSS of 300mm/s was also utilized in a different study by Awad et al., with KVA64 (all other parameters being kept the same) where ODTs with complex shapes and intricate surface patterns

were fabricated (See *Figure 2)* that also achieved disintegration times of ~4s as well as immediate drug release [38].

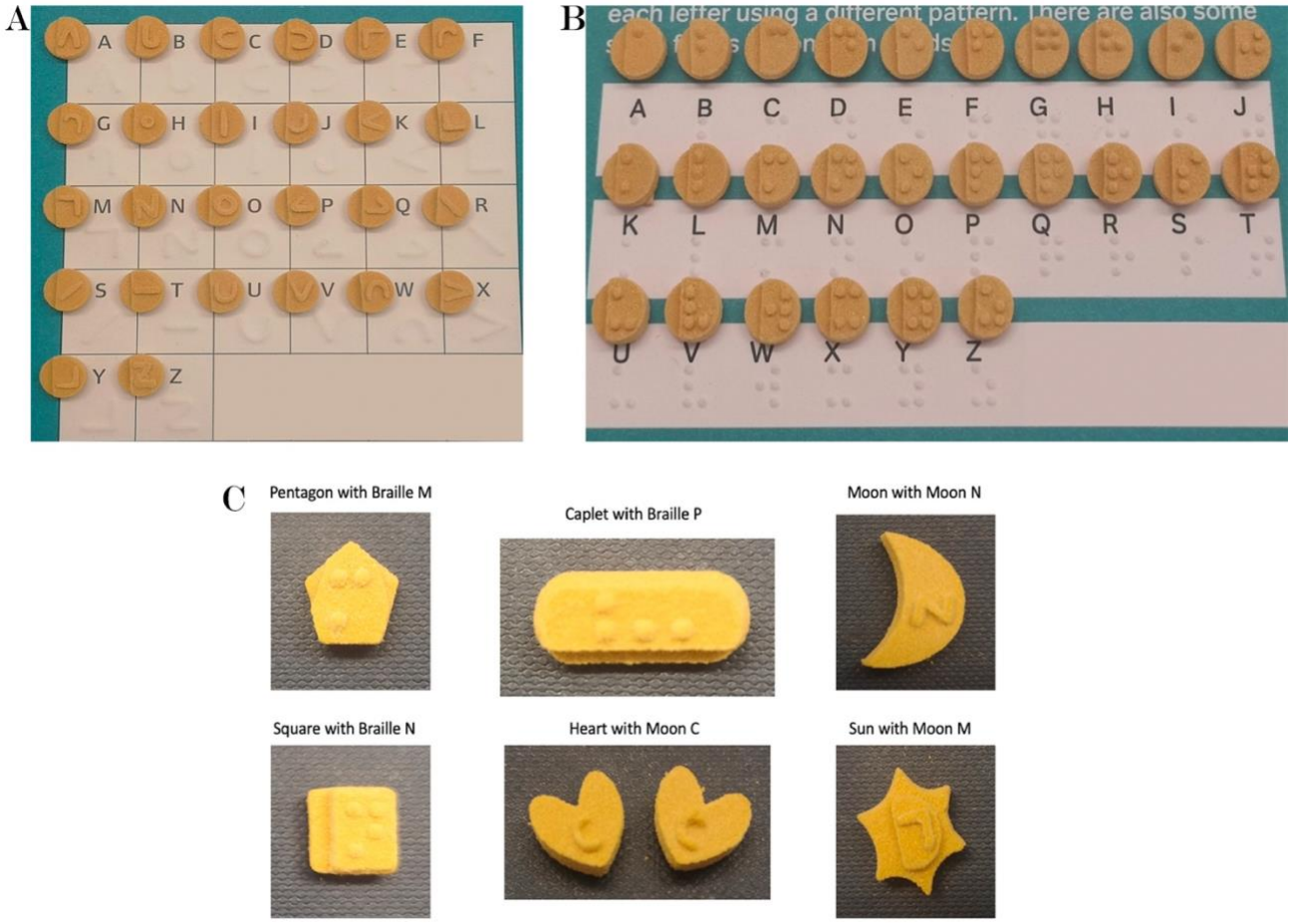

Figure 2: A) Cylindrical SLS manufactured ODTs containing 26 moon alphabet symbols on their surface [38]. B) Cylindrical SLS manufactured ODTs with 26 Braille alphabet indicators on their surface [38]. C) SLS manufactured ODTs with various shapes containing Braille and Moon alphabets on their surface [38]. The shape of the ODTs as well as the alphabet used reflect their intended purpose, with for example the moon shaped ODT and moon letter for N indicating that it is a dosage form that should be taken at night.

In a study by Allahham et al., manufacturing of KVA64 ODTs was investigated while using a minimal amount of the polymer in addition to using a drug encapsulation complex to taste-mask the API Ondansetron Hydrochloride, which reportedly has a very bitter taste, making difficult to use for pediatric patients [34]. Cyclodextrins (CDs) are cyclic oligosaccharides consisting of 7 D-glucopyranose units in the case of βCDs [39] with hydrophilic outer surfaces and a large cavity space capable of taking up a drug moiety thus increasing the dissolution properties of the drug as well as masking its taste.

Using the same printer and printing parameters as Fina et al., and Awad et al., [37,38] except for LSS of 200mm/s, 2 novel formulations were manufactured with the compositional difference between the two being the content of mannitol in the formulation (50 and 60% for formulation 1 and 2 respectively). These ODTs when incorporating Ondansetron containing βCDs in the formulation displayed accurate dosing of Ondansetron at 8 mg with no drug degradation. In this study reducing LSS which appears to be a crucial parameter regarding ODT manufacturing due to its influence on porosity did not hinder disintegration of dosage forms to the same extent as in above mentioned studies. Overall total porosity values of 37.1 and 41.5% for formulation 1 and 2 respectively were observed, with both formulations fully disintegrating in ~15 s with almost complete (~90%) drug release within 5 min [34]. It is hypothesized that reduction of LSS did not hinder disintegration and drug release properties necessary for ODT formations due to the incorporation of Mannitol as the primary component of the formulation. Mannitol has a T_m = 168°C, at printing temperatures of ~100°C it is hypothesized that Mannitol partially dissolves in the amorphous KVA64 whilst the rest of it remains unchanged within the polymer matrix, thus spacing the polymer chains making it highly porous. The highly porous morphology allows for inflow of media into the polymer matrix leading to surface erosion of the polymer and the release of the API [34].

Another taste masking study has been performed by Mohamed et al., investigating the incorporation of Clindamycin hydrochloride into ODTs [40]. Clindamycin hydrochloride, an antibiotic medication, reportedly not used in children due to its strongly bitter taste . As a solution, a pro-drug clindamycin palmitate hydrochloride (CPH) was formed, however in its powder form the drug is unstable from a long-term storage perspective and was reported to still retain its bitter taste [40]. Amorphous dispersion of CPH in the polymeric matrix of KVA64 to an extent resolves those issues and improves palatability. Due to the poor flowability of the drug (HR=1.4) [41] lactose monohydrate (LMH) was added to enhance flowability with similar results reported though incorporation of silicon dioxide [40]. Microcrystalline cellulose (MCC) known for its binding properties [42], was added to improve mechanical properties of the formulations such as friability. Similar to previous research, LSS was shown to have a significant impact on ODTs porosity, with LSS of 200mm/s resulting in total porosity values of ~24% and higher LSS of 300 mm/s yielding

total porosity of ~31% [40]. Additionally, incorporation of LMH was shown to have an impact on disintegration and dissolution of the ODT, as LMH has a higher Tm (144.2°C) than KVA64, it is hypothesized that at operating printing temperature LMH does not fully dissolve into the polymer matrix with some of its particles remaining unchanged and thus preventing sufficient molecular mixing, inadvertably increasing the porosity [40]. Incorporation of MCC had an opposite effect. Overall, however, amorphization of CPH was achieved in the polymer matrix and for formulations printed at a higher speed of 300mm/s with concentrations of LMH at 7.5% disintegration times of <2 min and drug dissolution of ~79% in 30 min were achieved [40].

Up to this point, all the above-described research was concerned with manufacturing ODTs using a diode laser, thus requiring the inclusion of a colorant absorbance enhancer, such as Candurin ® Gold Sheen, which gives the ODTs an unpleasant yellow color as well as taking up 3% of the formulation. Manufacturing of ODTs using a CO_2 laser with a 10.6 μm wavelength without an absorbance enhancer has been demonstrated by Gueche et al. Using a Sharebot ® SnowWhite 3D SLS printer (Sharebot,Nibionno, Italy), cylindrical ODTs of 10mm in diameter and 3mm height were manufactured using KVA64 as the main polymeric carrier while incorporating various Di-carboxylic acids in the formulation as well as Ibuprofen acid (IbuAc) (provided by Fagron, Rotterdam, Netherlands) and Ibuprofen sodium salt anhydrous (IbuNa) (Sigma-Aldrich, Saint-Louis, MO, USA) [35].

IbuNa is considered to be more soluble than IbuAc [43] but has a high T_m = 164.61°C. IbuAc on the other hand is poorly soluble and is susceptible to thermal degradation [35]. At 25% laser power as well as scan speed of 35,000 pps (2100mm/s equivalent) [44], incorporation of plasticizing excipients was investigated with the aim of decreasing the printing temperatures for formulations incorporating these API's. In this study Succinic Acid (SA) (see *Figure 3A)* has proven to be the most efficient plasticizer out of the 5 selected di-carboxylic acids [35]. The reason for its efficient plasticization is the presence of a carboxylic moiety that can act as a H-bond donating group and thus form H-bonds with the carbonyl functional group of KVA64 on the tertiary amide (see *Figure 3B)* [35]. Additionally in comparison to other di-carboxylic acids investigated, SA has a less rigid chemical structure with no double bonds in its polymer backbone as well as only having 2 hydroxyl functionalities per monomeric unit. It has been found that increasing the hydroxyl functionality in

the polymer chain has a negative effect on chain mobility where the excessive formation of H-bonds potentially restricts the chain movement in the polymer matrix while also increasing the molecular weight of the polymer, restricting the ability to diffuse into the pores in the matrix [35].

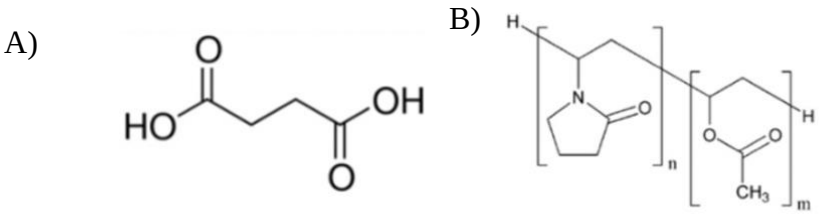

Figure 3: Chemical structure of a) Succinic acid, b) Vinylpyrrolidone-vinyl acetate copolymer (KVA64)[35].

With 5% API loading incorporation of IbuAc resulted in optimal printing temperature reduction of 40°C (from 110°C for KVA64 alone to 70°C) [35]. For IbuNa the optimal printing temperature remained at 110°C, most likely due to the absence of a H-bond donating carboxylic group compared to IbuAc. Lowering of the printing temperature for IbuNa was done by incorporating 5,10,15 and 20 (w/w) % of SA into the formulation. Incorporating 5,10,15 and 20% resulted in a decrease of printing temperature to 95,85,80 and 80°C respectively [35]. These values are the same as for the KVA64/SA formulations, indicating that no synergistic effect is achieved by mixing IbuNa and SA, with reducing of the printing temperature being a result of SA. T_g of all formulations were also analyzed, however multiple inconsistencies are present in the research regarding the incorporation of other excipients and their effect on T_g and printing temperature. This is most likely because obtaining T_g values for formulations was done by DSC which exposed the samples to much higher temperatures during the thermal history removal in comparison to temperatures used during printing. Therefore, the obtained T_g values are likely to be exaggerated.

Disintegration values for all KVA64/SA as well as KVA64/IbuNa/SA formulations at 5 and 10% loading of SA were below 30 s [35]. For 15 and 20% SA incorporated with IbuNa the disintegration values were elevated, most likely due to reduced porosity in the matrix from plasticizer saturation at 15% of SA. No degradation of the APIs occurred, showing that exposure of thermosensitive API to a CO_2 laser does not result in drug degradation [35].

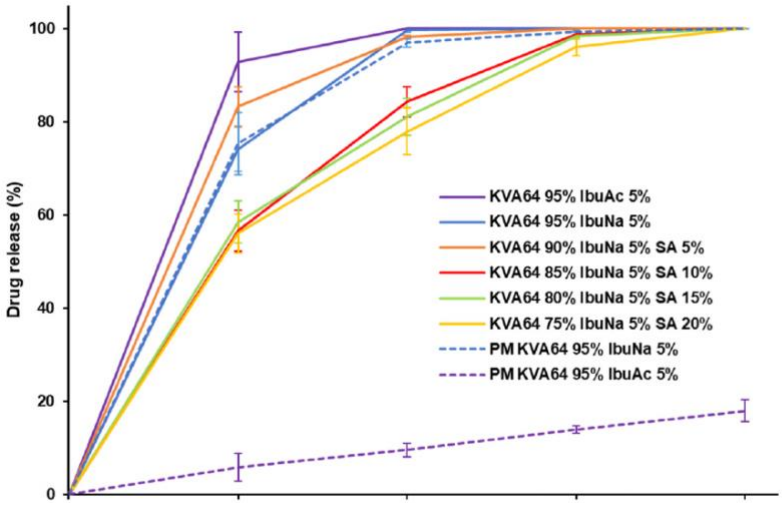

Figure 4 : Drug dissolution profiles of all manufactured ODTs as well as physical mixtures (PM) of IbuNa and IbuAc blended with KVA64 [35].

As seen in *Figure 4*, all SLS manufactured ODTs achieved 85-90% drug release within 15 minutes, with KVA64/IbuNa and IbuAc achieving 100% release in 10 minutes, making them all suitable as immediate release formulations [44]. Additionally, physical mixture (PM) of KVA64 and IbuAc only achieved ~18% drug release, showing that SLS can improve solubility of poorly soluble APIs though amorphous dispersion in the polymer matrix.

By looking at the success of KVA64 in ODT manufacturing and by looking at the shortcomings of polymer HPMC as the polymeric carrier it is clear that porosity of the polymer matrix is crucial in order to manufacture ODTs. Porosity to a large extent can be enhanced by increasing the LSS used however the polymer itself needs to have certain physiochemical parameters in order to manufacture ODTs suitable for pediatric applications. Using KVA64 as a reference, the following criteria should be taken into account when selecting polymers for ODT manufacturing.

1) The polymer particles must take on a spherical morphology as well as fit in the size range established in section 4, as KVA64 has the particle size of 71.5μm with a particle size range (PSD) of 2.16 with relatively good flowability [30].
2) The polymer should have a T_g of ~100°C, allowing it to be printed at low temperatures, preserving the API's.

3) The polymer should have a sufficient number of H-accepting functional groups, allowing to undergo plasticization if needed.

The chemical as well as morphological properties of KVA64 allow for formation of porous matrices where the API can be molecularly dispersed, and rapid disintegration can be achieved via the erosion of the polymer though the open pores

6. Minitablets

In ODTs the porous nature of the dosage forms was achieved due to the ability of SLS to loosely form bridges between the powder particles, allowing for fast dissolving dosage forms. While for ODTs this was achieved in large part due to the increased LSS the opposite can hold true for formulation of sustained release dosage forms that can be swallowed. By reducing the LSS and maintaining a relatively low printing temperature denser dosage forms can be manufactured. A study by Awad et al., using a 445nm 2.3W blue diode laser equipped SLS printer (Sintratec Kit, AG, Brugg, Switzerland) manufactured single and dual API minitablets of 1- and 2-mm diameters using Ethyl Cellulose N7 (obtained from Ashland, Schaffhausen, Switzerland) further abbreviated as EC as well as poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer Kollicoat Instant Release (obtained from BASF, Ludwigshafen, Germany) further abbreviated as KIR as polymer carriers [45]. The single particulate minitablets, composed of 92% EC, 5% Paracetamol (from Sigma-Aldrich, Poole, UK) further abbreviated as Par and 3% Candurin ® Gold Sheen (purchased from Merck, Darmstadt, Germany) as an absorbance enhancer. This minitablet displayed little visible porosity (see *Figure 5A)* and had drug dissolution of 88 and 61% after 24 hours for 1 and 2mm forms when tested with *in vitro* conditions simulating the acidic GI conditions as well as intestinal environments.

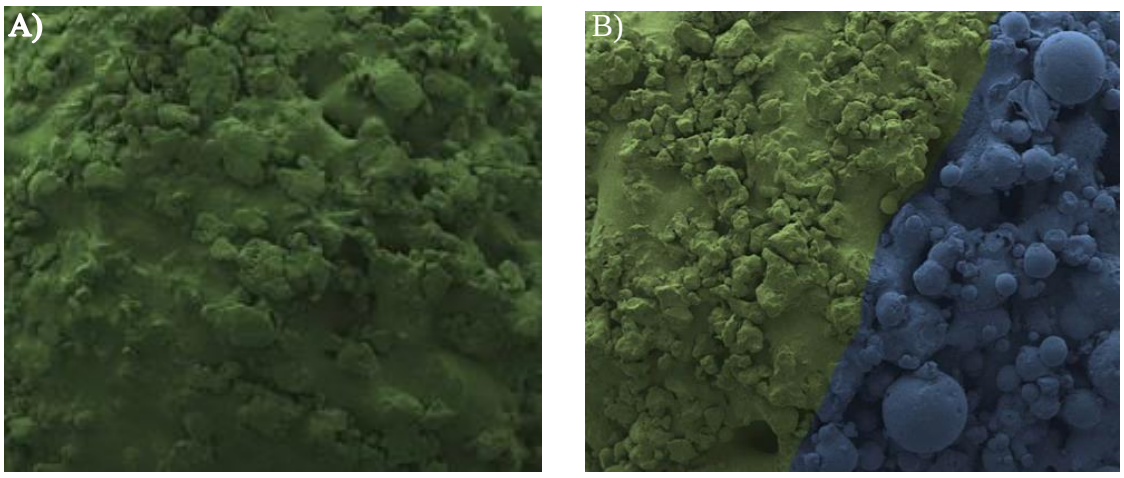

Figure 5: A) Scanning Electron Microscopy (SEM) image of 2mm diameter minitablet composed of Paracetamol as the API and Ethyl Cellulose (EC) as the polymeric carrier. B) Configuration B, consisting of Ibuprofen sodium salt (IbuNa) and poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (KIR), shown as the blue section as well as Paracetamol (Par) and Ethyl Cellulose (EC) shown as the green section [45].

Additionally, though polymer matrix manipulation, the compact miniprintlets were manufactured with 2 spatially distinct API's incorporated (see *Figure 5B)*, namely Par and

Ibuprofen sodium salt (IbuNa) (from Sigma-Aldrich, Poole, UK). Two configurations containing mixtures of Par (6.5%) and KIR (56.5%) as well as IbuNa (3.5%) and EC (30.5%) for configuration A and IbuNa (3.5%) with KIR (30.5%) and Par (6.5%) with EC (56.5%) for configuration B. Manufactured with the same printing conditions of LSS of 50 mm/s as well as chamber and surface temperatures at 100 and 120°C respectively, different drug dissolution profiles for 2 configurations were obtained (see *Figure 6)* [45].

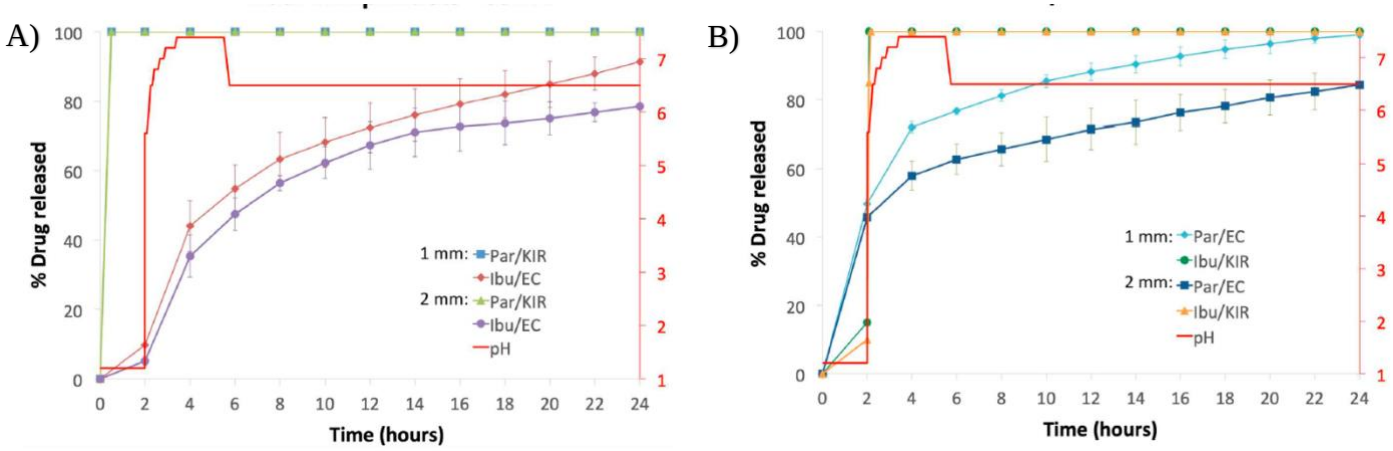

Figure 6: A) Drug dissolution data of Configuration A dual minitablet for 1 and 2mm diameters. B) Drug dissolution data of Configuration B dual minitablet for 1 and 2mm diameters. Red line for both graphs indicate the pH testing conditions with the first 2 hours simulating acidic GI conditions followed by more basic intestinal conditions [45]

From *Figure 6* it can be seen that overall KIR results in instant drug release while EC is more suitable for slower sustained drug release. It can also be seen that incorporation of IBU as a model API results in an initial lag when exposed to acidic conditions due to its insolubility in low pH [46]. No drug degradation was observed, and drug loading values were consistent with the theoretical formulations.

For successful formulation of mini tablets, incorporation of the API within the polymer matrix is necessary in order to allow for controlled release of the drug and to prevent premature drug release. In the study by Awad et al., selection of EC for sustained release formulations shows that chosen polymers need to undergo a relatively intense sintering process in order to be used. For EC this is a consequence of its morphology and potentially its chemical structure. Having irregular and plate like structures there is more surface area available for contact with nearby particles [45,46], allowing for formation of continuous melting pools of excipients, resulting in

void filling. The slow-release profile confirms this hypothesis as it indicates little porosity in the formulation as drug dissolution from EC polymers occurs though diffusion though the matrix pores [47]. Additionally, a possible explanation for the intense sintering of EC and APIs could be due to their chemical structures. For example, from *Figure 7* Par contains a hydroxyl group which can act as a H donating group and EC has ester functionality as well as a Nitrogen ion that can function as a H accepting groups. A possible explanation for increased sintering comes from the fact that Par would act as a plasticizing substance where via H-bond formation with EC the overall volume of the matrix will increase, resulting in an increased chain mobility thus requiring less energy density in order to achieve amorphization [47]. When the mobilization of chains is achieved with less energy density than required, excessive sintering occurs, and the molten polymer fills the porous voids in the matrix resulting in reduced porosity.

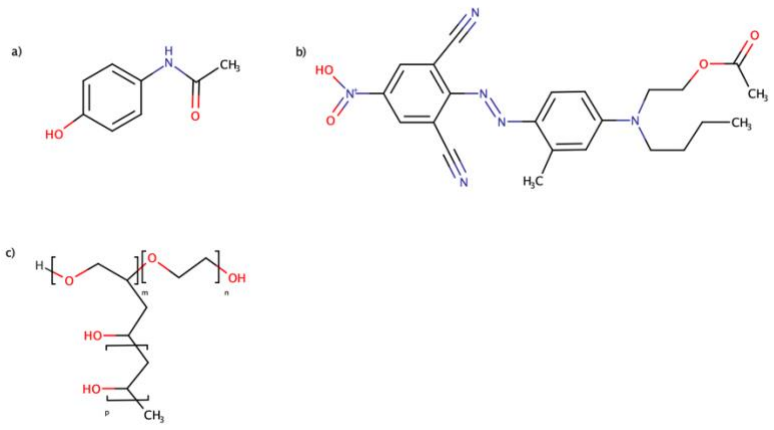

Figure 7: Chemical structures of a) Paracetamol , b) Ethyl Cellulose N7, c) Kollicoat IR

Use of KIR on the other hand results in instant release formulations as it established a more porous matrix structure due to its spherical particle morphology [45,48]. The shape that KIR particles assume does not have as much surface area to interact with nearby particles in comparison to EC and therefore results in more sintered rather than melted dosage forms. Additionally, from *Figure 7* KIR does not have as many H-bond accepting groups as EC does and hence API's will not induce plasticization to the same extent as they would with EC and so KIR undergoes a sintering process at lower intensity.

An important parameter for minitablet manufacturing for pediatric dosage forms is dosage uniformity. From this study it can concluded that perhaps polymers with a more uniform morphology should be considered. This conclusion is derived from the fact that in PAR/EC formulations PAR (Tm = 168°C) is still present in its crystalline form. This is visible from

Figure 5B where large plate like structures indicative of Par are visible. Additionally in *Figure 6B* Par undergoes accelerated release from the EC, this is possibly due to the fact that a large proportion of Par is present on the surface and is not fully incorporated in the polymer matrix, possibly due to limited porosity because of the morphology of EC.

Overall, manufacturing of mini tablets as dosage forms is possible. These mini tablets meet the minimal dosage requirements for pediatric formulations as they can be used to manipulate the drug release profiles by using different polymers and though polymer matrix manipulation formation of dual API systems is possible, thus minimizing the need for frequent medication intake as well as allowing for adjustable dosage though taking different numbers of the mini tablets. The size of the manufactured mini tablets also meets the acceptability requirements for pediatric populations.

7. Tablet formulations

As previously stated, outside of mini tablets and ODTs tablet formulations as dosage form also hold value for pediatric populations. With this being a preferred and highly accepted dosage form amongst the adolescent population [24].

Manipulation of release profiles for tablets has been demonstrated in Fina et al., where gyroid lattice containing tablets were manufactured [47]. Due to the nature of SLS, allowing for fabrication of complex overhanging structures, intricate morphologies can be made as can be seen in *Figure 8A.* Here due to the increase in surface area and much higher porosity in comparison to the cylindrical counterparts the medium that the formulations are exposed to is able to penetrate the polymer matrix much easier, thus resulting in accelerated dissolution rates. Additionally manufacturing of novel bi-layer structure was demonstrated (see *Figure 8B)* where due to the differences in porosity and overall surface area, modified release behavior can be obtained, with instant burst release from the lattice structure followed by sustained release from a conventional surface [47]. This demonstrates the flexibility of the SLS process as well as the limitless possibilities of formulations when it comes to disintegration and drug release as different matrix compositions as well as different polymeric materials can be used to tailor precise release kinetics of the API. These specific formulations may not be applicable to pediatric patients due to rough surfaces of the gyroid structures however it could be possible the utilize the bi-layer principle for manufacturing of more child friendly tablets with less bulky topography.

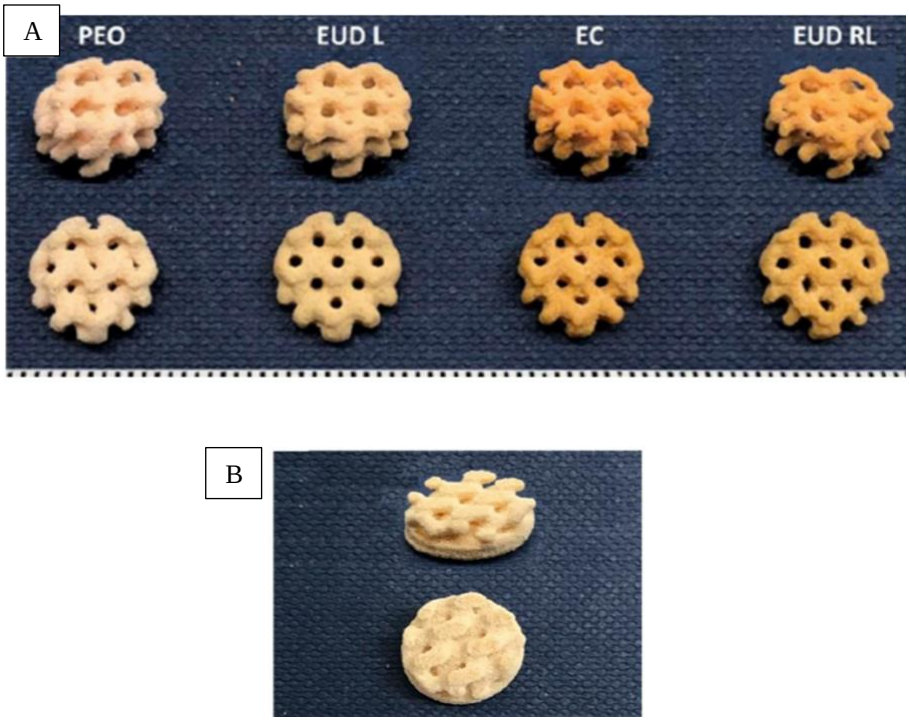

Figure 8: A) SLS printed 3D gyroid lattice dosage forms with different polymeric carriers. B) SLS 3D printed bi-layer structure using Polyethylene Oxide (PEO) as the polymeric carrier [47].

As mentioned in section 3, one of the common issues for adherence to medication in pediatric populations is dosage frequency. A possible solution for this was investigated by Kulinowski et al., where high API dosage loading without significantly increasing the weight of the formulation was done by manufacturing a dosage composed mainly by the API (~95%) [49]. This study was one of few [50] to also investigate the impact of scan spacing, also known as hatch spacing on energy density while keeping the LSS constant at 100mm/s with layer thickness of 100 μm and the chamber and surface temperature being 140 and 150°C respectively for the optimized formulation. 2 formulations with different SA/V were investigated (See *Figure 9).*

The paracetamol API (ATABAY Inc. Turkey) had a broad particle size distribution with the largest particles having diameters of ~350um and the smallest being only a few μm [49]. Majority of the powder volume was composed of particles in the ~50-200 μm. Evaluating 3 different hatch space (HS) sizes, namely 150, 100 and 50 μm, it was found that decreasing the hatch spacing results in an increase in energy density. This was shown though SEM evaluation where the dosage form made with HS150 resulted in sintered Paracetamol regions when compared to raw powder. For HS100 and HS50 the printlet surfaces were more uniform, with smaller paracetamol grains visibly undergoing melting where they are internalized on the surfaces of larger grains. Increasing the

energy density has overall impacted the internal morphology of the printlets, with relativelly uniform internal porosity of HS150 dosage forms being changed to denser matricies, with far less porous networks, with the upper area of the HS50 printlet having porosity of 1% in comparison to 30% for HS150 [49].

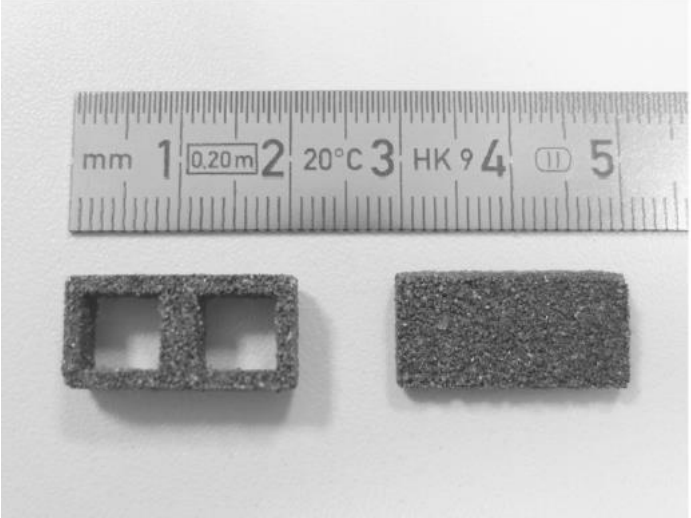

Figure 9: Picture of SLS manufactured dosage forms with different SA/V ratios 2.1 for hollow brick formulation (left) and 1.3 for solid brick formulation (right) [49].

Though drug dissolution profiles this study has found that modifying the SA/V ratio has a large impact on API release as the hollow brick structure manufactured at HS150 released 70% of the API in 0.75 h, while the solid brick took 2 h to release the same amount. Additionally it was found that modifying internal geometry of the dosage form also has an impact on drug dissolution, evident from the fact that the hollow brick manufactured at HS150 took 0.75h to release 70% of API while a hollow brick at HS50 took 4h [49]. While these dosage forms may be too large to swallow (20 x 10 x 5.6mm), modifying drug release via change in hatch space as well as the surface area of the dosage form can prove to be useful in future studies. Additionally, the possibility of making pure API dosage forms alleviates the need to manufacture heavy dosage forms that are required for high API load [49].

8. Future research

Presented research demonstrates that there are multiple ways to influence the release profiles of the incorporated APIs, whether that is though altering of the LSS, hatch/scan spacing or the selection of the polymer. This presents a myriad of possibilities for tailor made dosage forms, where dosage forms can be made with multiple different internal and external geometries, containing different APIs, thus allowing for tailored drug release of specific APIs in one dosage form.

For minitablet formulations to the author's knowledge only the study by Awad et al., has investigated minitablet manufacturing using SLS. Possible future research could be focused on attempting to make oro-dispersible minitablets as this could resolve the fears of some children associated with swallowing of multiple minitablets, with some children saying that they are scared that they may get stuck in their gums or tonsils [24]. Formation of oro-dispersible minitablets could be achieved through manipulation of energy density though increasing laser scanning speed as well as scan/hatch spacing, but also by incorporating certain spacing excipients such as mannitol or lactose monohydrate, which if printed at lower temperatures can increase the porosity of dosage forms, as shown for ODTs.

More research must be done in regard to manufacturing using a CO_2 laser. One of the biggest concerns regarding this laser was API degradation. However, the limited literature available has shown that no drug degradation occurs and though inclusion of plasticizers the API can be shielded. It is possible that CO_2 manufacturing is most suitable for ODTs due to its high printing speed. However, though incorporation of binders such as microcrystalline cellulose or though usage of high molecular weight polymers with tightly spaced matrices it could be possible to manufacture more compact dosage forms.

Lastly, children have reported to have a dislike of the grainy textures of SLS dosage forms [29]. Future research could try to incorporate post processing procedures such as vibratory polishing [51] to improve the surface of the dosage forms and assess the acceptability in pediatric populations.

9. Conclusion

This review demonstrates the suitability of SLS as a manufacturing method for fabrication of pediatric dosage forms. Reviewed literature demonstrates the ability of SLS to manufacture dosage forms that meet the specific needs of pediatric populations. Adjustable dosage forms can be achieved though manipulation of energy density determining parameters such as laser scanning speed and scan space as well using different polymeric carriers. Polymers with spherical morphologies and a relatively small size, when printed at high speeds result in formation of highly porous matrices due to exposure of particles to low energy from the laser. These formulations are suitable for manufacturing of oro-dispersible dosage forms, accepted by the pediatric population as they do not have to be swallowed. With large majority of all investigated ODTs meet the disintegration requirements set by the FDA and European pharmacopeia as they disintegrate within 30 seconds and have sufficient breaking properties necessary for dosage form handling. Using lower scanning speeds, smaller scan/hatch spaces as well as choosing polymers with more irregular and coarse morphologies with more functional groups allowing for plasticization can result in denser dosage forms suitable for manufacturing of minitablets.

Palatability issues can be resolved via SLS though amorphization of drug complexes in the highly porous polymer matrix as well as via inclusion of large sugar molecules that can take up the API in the cavity, while simultaneously not impacting the disintegration and dissolution within the polymer matrix, possibly due to the inclusion of spacing excipients with thermal properties too large for the printing process.

Minimal dosing frequency can be achieved though incorporation of 2 spatially different APIs in 1 dosage form, though the manufacturing of high dose API as well as though utilization of polymers with different chemical and morphological properties that due to different porosities result in different release profiles as well as though manipulating the surface area of the dosage forms by changing its shape.

Throughout there have been no mentions of drug degradation due to the use of the laser or the optimized printing temperature. With inclusion of plasticizers even showing an API shielding mechanism though lowering of the printing temperature. Moving forward there are many avenues

for future research. Majority of the studies in the field have been done using a blue diode laser due to the concerns regarding degradation of the API using a CO_2 laser. This so far does not seem to be the case, however that obviously depends on the API used. Nevertheless, more research must be conducted using a CO_2 laser to fully explore the possibilities of SLS printing. There also seems to be a limitless number of configurations to be explored due to the flexibility of the SLS. Various multi-layered dosage forms with different geometries, possible incorporation of multiple APIs and use of different polymers with different internal structures, allowing for dosage forms with multiple independent drug release profiles.

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