Selective laser sintering as a method of tablet preparation.

Selective laser sintering (SLS) is one of the 3D printing methods that is currently being developed and applied in many areas of our life. It is also starting to affect the preparation of pharmaceutical dosage forms, where it is mainly used in the field of solid dosage forms, mainly tablets. The creation of an object using SLS is based on joining powder particles using a laser beam, which sinters the individual particles together in individual layers. The strength of the bonds between the particles, and therefore the product, can be influenced by the speed (LS) and laser power (LP), the height of the layer (LT), or by changing the amount of supplied energy (ED) that acts on the powder at the point of connection and can be calculated according to the following formula (1):

ED [J/mm3] = LP/ (LS x HP x LT) (1)

HP – laser path distance

SLS is a one-step process, unlike the FDM 3D printing method, where a filament containing a polymer and a drug must be prepared first, specifically by extrusion. The limit of the method is the absorbance of the used material for the laser beam. This problem is solved by adding pigments with high absorbance for a given laser spectrum. Another limitation of the SLS method is the impossibility of using light-sensitive and thermolabile substances. A disadvantage can also be poor stability, application errors, and an unpleasant taste. The benefits of the method are obtaining objects, in our case tablets, of different sizes and shapes, with the possibility of setting different rates of drug release, disintegration time, etc. These properties are mainly due to the possibility of regulating the porosity of the tablets by laser speed but also by the composition of the given formulation. This method cannot yet match the productivity of standard methods of tablet production, especially conventional compression. Still, it allows for the individualization of the preparation of tablets in small batches with the aim of personalizing pharmacotherapy.

Excipients

SLS uses thermoplastic polymers as drug carriers. The printing temperature is set below the melting temperature of semi-crystalline polymers or below the glass transition temperature of amorphous polymers. Among the most commonly used polymers is copovidone (Kollidon VA 64), which has a low glass transition temperature (approx. 105 °C), which enables a lower

process temperature and also preparation of orally disintegrating tablets. Other polymers include semi-crystalline PEG-PVA (Kollicoat IR), HPMC, EC, Eudragit, and polyethylene oxides. Printing with amorphous polymers produces softer and more porous tablets with a rough surface, while semi-crystalline polymers show a dense, less porous structure and a smooth tablet surface. The sintering process can be improved by the addition of polymers with low melting or glass transition temperatures. In addition to the suitability of thermal properties, these polymers must also ensure good flowability, which is a reflection of the physical characteristics of the powder, e.g., particle size and shape, surface roughness. Other important auxiliary substances are colorants, as polymers are unable to absorb laser light at a wavelength of 445 nm. The most commonly used dyes are Candurin® Gold Sheen and NXT Ruby Red. The use of Gold Sheen dye is now being debated, as this dye contains approximately 50% titanium dioxide, which should be replaced in the future due to the potential carcinogenicity. The Ruby Red dye is therefore more promising, as it contains approximately 50% of silicon dioxide and 50% of red iron oxide. The properties of tablets prepared by 3D printing can be further modified by the addition of other auxiliary substances used in conventional compression, such as fillers, e.g., lactose, mannitol, and microcrystalline cellulose with the aim of improving some properties. Furthermore, the flowability of the powder can also be improved using talc or colloidal silicon dioxide. A superdisintegrant, e.g., crospovidone, can also be added for potential faster tablet disintegration. However, none of these auxiliary substances must negatively affect the sintering process.

Active pharmaceutical ingredients (API)

SLS can affect the physical state and release of the drug, as well as contribute to its thermal degradation if the drug substance is highly thermolabile. In the Sintratec Kit device, the laser has a low and constant intensity of 2.3 W, which reduces the possibility of thermal degradation of the drug, e.g., unlike a device with a CO2 laser, whose intensity is significantly higher. This 3D printing method is also more advantageous for high-dose drugs, when the polymer in the tablet is less than 30%, and such tablets prepared by the FDM method are very fragile and therefore unpreparable. The combination of two thermal processes, heating before and during the sintering process, can lead to the preparation of an amorphous solid dispersion (or solution), which will promote the solubility of poorly soluble drugs.

SLS procedure on a Sintratec kit printer (AG, Bruges, Switzerland):

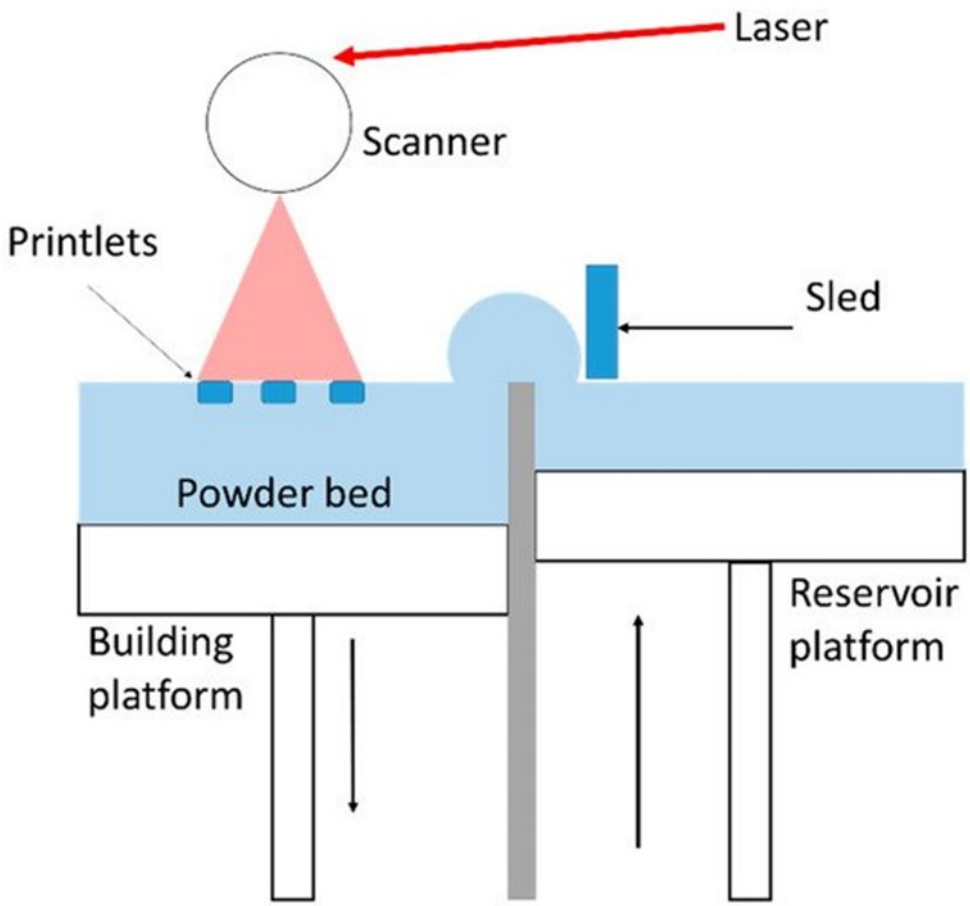

Fig 1: Schematic of the SLS printer

The first step is the preparation of the material for printing: a mixture of excipients and drugs, from which the tablets will be printed. The next step is the preparation of a stereolithography file using software where a 3D object, its dimensions (X, Y and Z axes) and shape are modelled in a suitable program, for example CAD, and saved in a STL format. This file is then ready for the transfer to the printer and the printing process is carried out according to the G-code generated by the STL format. Subsequently, the printer is filled with powder. The printing platform must be moved to its highest position and the reservoir so that it will be possible to insert the amount of powder required for the entire printing process. After filling the chamber and soothing the printing surface, the model for the printing is inserted using the software. Afterwards, we set the printing parameters, namely the heating temperature of the printing chamber, the temperature of the powder surface, the laser speed and the height of the layer.

After confirming the entered parameters and uploading the model, the chamber and the powder will be heated using heating spirals and halogen fluorescent lamps. The temperature is continuously controlled using thermistors and IR sensors. After the uniform heating of the chamber, the software starts the preparation of the printing surface by aligning the powder and then the printing itself using a blue diode laser (445-450 nm).

Printing takes place in layers. The process of printing one layer is as follows: A modelled layer is sintered onto the prepared, homogeneous, flat printing surface, which is connected to the previous layer located below it. Alternatively, it may be the first layer of the print, after which there is no connection to the previous layer. When the object is finished, the print platform moves downwards by one layer height, and the storage platform moves up by the corresponding amount of material. Subsequently, the sliding arm covers the printed layer with a new powder from the chamber. Excess powder falls over the edge of the printing chamber into the designated space. A new printing layer is thus prepared again, and the whole process is repeated. After the entire print is completed, the objects are covered with several layers of powder, and the printer starts to cool down automatically. It is also possible to prepare tablets in another layer of already heated powder, even with the setting of other printing parameters. After cooling, the finished products are removed and the unused unbaked powder from the printing chamber. The powder can usually be recycled once after checking with DSC. However, it is advisable to sieve it or dilute it with new powder in a ratio of 3:7.

Fig. 2: SLS printer Sintratec Kit

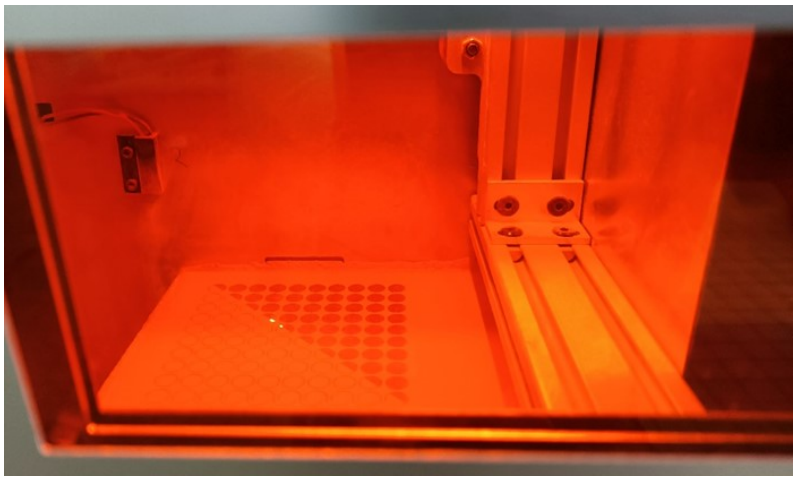

Fig. 3: Tablet printing by laser

Variability of tablet structure

3D printing makes it possible to create objects of different geometries, while this ability regulates the dissolution profile of the drug in the final tablets.

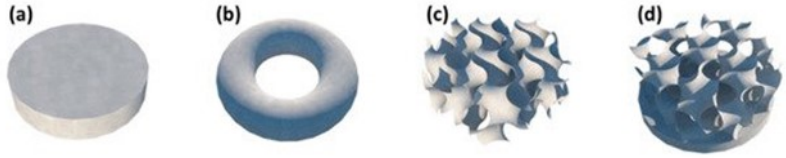

Fig. 4: Design examples of tablets prepared by SLS: (a) cylindrical (b) annular, (c) gyroid grid, (d) double layer cylindrical and gyroid

The large specific surface area of the gyroscope grid leads to rapid tablet erosion and rapid dissolution. On the contrary, the combination of this lattice and the cylindrical shape leads to a moderate rate of drug release. Also interesting are tablets with channels, the design of which also accelerates the release of the drug. On the contrary, by using a water-insoluble polymer, e.g., ethyl cellulose, matrix-type tablets with prolonged drug release can be prepared. The internal structure of the tablets is not only determined by the pre-set model, but also by the printing parameters. The speed of the laser affects the size and formation and distribution of the pores in the tablet. Porosity is a critical parameter for disintegration time and thus drug dissolution and availability. The high power of the laser or its low-speed lead to the formation of narrow internal channels in the tablet and thus to a prolonged release of the drug. The temperature of the powder is also important for controlling the porosity, which is inversely proportional to the resulting porosity of the tablets. Material parameters are also important, as polymers with a high melt flow index provide structures with higher density and thus lower

porosity. Particle size is also important, as finer particles (106 – 150 μm) increase the contact area, which results in a higher degree of sintering and lower porosity.

The addition of various substances, e.g., fillers such as lactose, mannitol, leads to more porous tablets due to their higher melting point.

Possibilities to influence tablet properties

Tablet strength decreases with increasing laser speed and decreasing printing temperature, which is also related to increasing porosity. This is advantageous for orodispersible tablets. Incorporation of other excipients into the polymer matrix also affects the mechanical properties of the tablets by interfering with the internal structure of the tablets. The presence of lactose reduces mechanical strength, while microcrystalline cellulose increases it. The properties are also affected by the presence of drugs, e.g., ibuprofen has a strengthening effect due to the intensification of sintering. Particle size is also important. Finer particles reduce porosity and increase strength. The sintering process is more perfect. Higher porosity also accelerates drug release. Tablets prepared at higher laser speeds from erodible polymers (Kollidon VA 64) quickly disintegrate into many fragments that increase the specific surface area and lead to faster dissolution. E.g., the combination of Kollidon VA 64 with paracetamol led to a disintegration time of more than 600 s at a laser speed of 100 mm/s, after increasing the laser speed to 300 mm/s the disintegration time was up to 4 s. The temperature of the chamber is also important for the porosity and thus for the release rate of drugs. With its increase, the porosity is lower, and thus the drug release rate is slower.

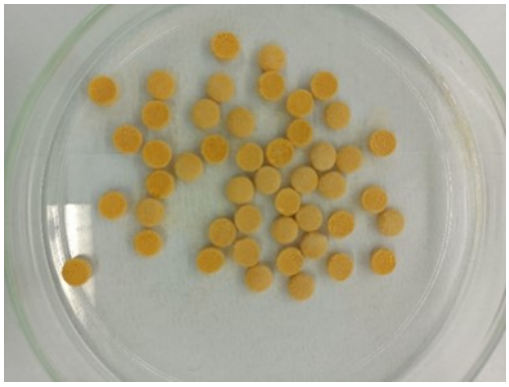

Fig. 5: Tablets from polymer Kollidon VA64 with the colorant Gold Sheen

Gueche, Y.A., Sanchez-Ballester N. M., Cailleaux S., Bataille B., Soulairol I: Selective laser sintering (SLS), a new chapter in the production of solid oral forms by 3D printing. Pharmaceutics 2021, 13, 1212.