Three-dimensional Printing of Ramipril Tablets by Fused Deposition Modeling

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Abstract
Introduction. Arterial hypertension is one of the main risk factors for the development of cardiovascular diseases. Drug treatment of arterial hypertension is associated with a number of difficulties: often requires combination therapy, also a possible change in either dosages or drugs during treatment during the patient’s life. Three-dimensional printing allows to create individual medicines on-demand.

Aim. Study suitability of Kollidon® VA 64 as a matrix-polymer for the preparation of immediate release ramipril printing tablets.

Materials and methods. Substance: ramipril; excipients: Kollidon® VA 64, Kollidon® CL-F, Soluplus®, PEG 1500, sodium carbonate anhydrous, Poloxamer 188, sodium stearyl fumarate, mannitol; reagents: hydrochloric acid, acetonitrile for ultra-HPLC, sodium octanesulfonate for HPLC, orthophosphoric acid 85%, sodium perchlorate analytical grade, triethylamine, standard: ramipril USP (№1598303). Ramipril filaments were prepared by hot melt extrusion on the extruder Haake™ miniCTW (Thermo Fisher Scientific). The tablets were printed on a hand-made 3D printer. The printlets were studied for friability and hardness. Uniformity and quantitative determination of ramipril and impurities in tablets and filaments were determined by high performance liquid chromatography on a Shimadzu Prominence LC liquid chromatograph. Stability of ramipril was studied on a DSC 3+ Mettler Toledo by differential scanning calorimetry. Also, the stability of ramipril was determined by the Raman spectroscopy on an analytical system ORTES-785TRS-2700.

Results and discussion. Ramipril filaments with a diameter of 1.75 mm were obtained by melt extrusion at a temperature of 105 °C. They were homogeneous in quantitative content of the active substance. From the resulting filaments, tablets were printed in five configurations with three filling densities: 30%, 50% and 100%. Degradation of ramipril in filaments and tablets is not observed. The melting point of the selected mixture is lower than the melting point of matrix-polymer. It makes possible to lower the processing temperature. Tablets with 100% filling provide an immediate release of ramipril.

Conclusion. Kollidon® VA 64 is suitable as a matrix-polymer for the development of immediate release ramipril printlets. Kollidon® VA 64 provides the necessary physical and processing properties of the filament required for FDM printing.

Keywords: hot melt extrusion, filament, fused deposition modeling, three-dimension printing, additive manufacturing, personalized medicine, printlets, ramipril

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Oksana A. Terenteva and Konstantin A. Gusev developed and carried out the experiment. Viktoria V. Tikhonova determined the concentration of the ramipril by HPLC. Georgiy A. Shandryuk carried out the thermal analysis. All authors participated in the discussion of the results and wrote the manuscript.

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INTRODUCTION

Three dimensional (3D) printing techniques have been intensively developed and integrated in various industries over the past ten years. In the design of pharmaceuticals, 3D printing is attracting the growing wave of emphasis as that technology solves some of the problems faced by traditional production. For instance, the manufacture of tablets involves several successive process steps: milling, mixing, pelleting, and compression which can yield a finished product of unstable quality. 3D printing has offered unprecedented flexible design and fabrication of complex products that can be used for the implementation of personalized medicine.

Different industries utilize 3D printing as the technology enables production of individual objects with the required shape and configuration on-
demand. In pharmaceutical industry, 3D printing is used in the development of personalized drugs [1, 2], orphan drugs [3, 4], modified release systems [4–6] and polypills [7–10]. Fused deposition modeling (FDM) is one of the most common methods of 3D printing in pharmaceutical technology.

FDM printing 3D is the technology creating a three-dimensional object of a specified geometric shape by sequential deposition of layers of melted or softened thermoplastic materials compressed through the 3D printer’s heated nozzle. FDM printing obtains drug products containing a strictly specified amount and distribution of the active substance, dosage forms of a necessary size, shape, geometry, density and filling which can be easily changed. The raw materials for FDM printing are usually provided as filaments which are produced with the hot-melt extrusion (HME). The pharmaceutical application of this technology is limited to the shortage of filaments consisting of materials suitable for medical use. Filament fabrication has become an important area of pharmaceutical investigations due to the increasing interest in the FDM printing. The raw materials for the manufacture of filaments are approved polymers for pharmaceutical use (polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, etc.) [6].

HME of compositions polymer-active pharmaceutical ingredients (API) is the main technique for production filaments for 3D printing. The API is incorporated into the polymer matrix during the melting process. The disadvantages of this method are the following: heating which limits the use of thermolabile API; low printing speed; and the difficulty of equipment cleaning. Although the HME has some limitations, it is simple and versatile, and is widely used for filament development and three-dimensional printing of pharmaceuticals.

Ramipril is an angiotensin-converting enzyme inhibitor prescribed for the treatment of arterial hypertension. Ramipril tablets on the Russian pharmaceutical market are presented in 2.5 mg, 5.0 mg and 10.0 mg doses, while a dose change is required depending on the blood concentration of potassium and the concurrent administration of diuretics [11]. Therefore, ramipril is a good object for the development of personalized dosage forms with different doses.

**Aim.** Study suitability of Kollidon® VA 64 as a matrix-polymer for the preparation of immediate release ramipril printing tablets.

**MATERIALS AND METHODS**

API: ramipril CJSC "Active Component" (Russia); ingredients: Kollidon® VA 64 polyvinylpyrrolidone and vinyl acetate copolymer (BASF, Germany), Kollidon® CL-F crospovidone (BASF, Germany), Soluplus® (BASF, Germany), polyethylene glycol (PEG) 1500 (Merck, Germany), anhydrous sodium carbonate (Dr. Paul Lohmann, Germany), Poloxamer 188 (Merck, Germany), Alubra™ PG-100 (FMC BioPolymer, USA), mannitol 100 SD Pearlitol (Roquette, France); reagents: hydrochloric acid (Kaustik, Russia); acetonitrile for ultra HPLC (J. Baker, The Netherlands); octanesulfonate sodium for HPLC (Panreac, Spain); orthophosphoric acid 85% LiChropur® (Merck, Germany); perchlorate sodium (Sigma-Aldrich, USA); triethylamine (Biochem, France); USP standard sample of ramipril (№1598303).

**Equipment.** Haake™ miniCTW laboratory twin-screw extruder, Thermo Fisher Scientific (Germany) with oppositely directed conical screws; electronic digital vernier caliper; Erweka DT 626/1000 HH dissolution tester (Germany); Erweka TBH 125 TDP hardness tester (Germany); Erweka TAR 220 tablet friability tester (Germany); HPLC chromatograph Shimadzu Prominence (Japan), diode-matrix detector, Shim-pack GIST 250×4. 6 5µm C18; analytical system of raman scattering ORTES-785TRS-2700 (“OPTEC”®, Russia); 3D printer; differential scanning calorimeter DSC 3 3+ Mettler Toledo (Switzerland); scanning microscope Phenom XL Thermo Fisher Scientific (USA).

**Ramipril filament production.** Ramipril and excipients were mixed manually using a mortar and pestle, and dusted with sodium stearyl fumarate. The prepared mixture was loaded into the extruder feeder and then extruded at constant temperature through a 2.0 mm diameter nozzle at screw speed of 20 rpm.

**3D printing of ramipril tablets.** The tablets were printed from filament by FDM printing (Figure 1). A digital model of the tablets was designed with KOMPAS-3D version 15.1 by Ascon (Russia) and exported as a *.stl file. The model was sliced in Ultimaker Cura slicer (version 4.6) and was carried out with Repetier-Host program (version 2.1.6).

The printing parameters and G-code version were set according to the Prusa i3 model. The process parameters are shown in Table 1.

The tablets were printed on a heating platform covered with a polymer film 0.3 mm thick.

**Morphology.** The tablet diameter and thickness were detected by an Erweka TBH 125 TDP tablet hardness tester. The filament diameter was measured with an electronic digital vernier caliper. Pictures of the devices were taken with an Olympus OM-D E-M1 camera.
Tablet friability test was carried out according to GPM.1.4.2.0004.15 (The State Pharmacopeia of the Russian Federation) by the Erweka TAR 220 tablet friability tester.

The tablet hardness was checked in the ERWEKA TBH 125 TDP tablet hardness tester.

**Dosage uniformity of the filament.** The accurately weighed amount of filament was taken and dissolved in phosphate buffer. The quantitative content of ramipril in the filaments was defined with HPLC.

**Raman spectroscopy.** Raman spectroscopy was carried out on analytical combination light scattering system ORTES-785TRS-2700. Laser radiation power was 100 mW, exposure time – 60, 90 and 120 s. The spectral data was recorded with specialized software BWSpec 4_10.4.

**Thermal analysis.** The thermal analysis was performed on a differential scanning calorimeter DSC 3+ Mettler Toledo.

The method consisted of three consecutive operations: heating, cooling, heating in the range of 0 to 150 °C. The temperature was changed with intensity of 10 K/min, in nitrogen medium with a flow rate of 50 ml/min. Standard perforated 40 µl aluminum pans were used. Temperature and enthalpy calibration was made with pure metals, indium (ME-119442) and zinc (ME-119441), according to the producer’s instructions. The data was analyzed with Mettler STARe software version V16.20c.

**Dissolution testing.** Dissolution profiles were obtained using a USP-I apparatus. In each assay, the printlets were placed at the basket in 0.1N HCl pH = 1.2 (500 ml) under constant rotational speed (50 rpm) at (37.0 ± 0.5) °C. Sampling points: 3, 5, 10, 15, 30 and 45 minutes. The selected sample in the amount of 5 ml (the volume of medium was compensated by the same solvent) was filtered over a membrane filter (RC) with a 0.45 µm pore diameter.

The drug concentration was determined with HPLC. For this purpose, 100 µl of the solution was filled into the chromatograph injector, chromatographed under the isocratic elution mode: speed 0.5 ml/min, column

| Parameters                 | Value  | Parameters                 | Value  |
|----------------------------|--------|----------------------------|--------|
| Tablets shape              | Cylinder | Nozzle size, mm          | 0.6    |
| Tablets diameter, mm       | 10     | Filament diameter, mm     | 1.75   |
| Layer height, mm           | 0.3    | Flow, %                   | 110    |
| Initial layer height, mm   | 0.3    | Retraction distance, mm   | 3      |
| Line width, mm             | 0.6    | Retraction speed, mm/s    | 50     |
| Wall thickness, mm         | 1.2    | Print speed, mm/s         | 10     |
| Top layers, pcs            | 1      | Infill density, %         | 20, 50 |
| Bottom layers, pcs         | 1      | Pattern of cap/bottom infil | Line |
| Nozzle temperature, °C     | 105    | Infill pattern            | Grid   |
| Skirt/brim speed, mm/s     | 5      | Build plate temperature, °C | 65     |
| Infill speed, mm/s         | 10     | Number of brim            | 3      |
| Initial layer speed, mm/s  | 5      | Enable print cooling, %   | 0      |
| Wall lines, pcs            | 2      | Wall speed, mm/s          | 10     |
| Build plate adhesion type   | Brim   | Travel speed, mm/s        | 150    |
thermostat temperature 25 °C, retention time of ramipril was approximately 16.5 min.

Preparation of the mobile phase: 0.1% sodium octanesulfonate solution (pH = 2.4) was mixed with acetonitrile in a ratio 550:450. The acidity of the obtained solution was 2.75. The pH was adjusted with orthophosphoric acid.

The controlled ramipril impurity, the main degradation product that is formed during ramipril cyclization, is ramipril-diketopiperazine (impurity D), which is generated in an acidic environment under heating. The analysis was made with HPLC on a Shimadzu Prominence LC liquid chromatograph (diode-matrix detector, Shim-pack GIST 250 × 4.6 5 μm C18 column), detection wavelength 210 nm. The analysis methods: 0.1 g (accurately weighted amount) of the tested object was dissolved in phosphate buffer (pH = 6.86), 100 µl of the solution was introduced into the chromatograph injector, chromatography was performed in gradient mode of elution, the rate was 1 ml/min, thermostat temperature was 65 °C, retention time of ramipril approximated to 18 min, relative retention time of impurity D reached 1.6.

The mobile phase consisted of solutions A and B. Solution A was prepared by dissolving 2.0 g of sodium perchlorate in 800 ml of purified water, adding 0.5 ml of triethylamine, adjusting the pH of the obtained solution with orthophosphoric acid up to 3.6, adding 200 ml of acetonitrile. Preparation of solution B: 2.0 g of sodium perchlorate was dissolved in 300 ml of purified water and 0.5 ml of triethylamine, the pH was adjusted up to 2.6, 700 ml of acetonitrile was added.

RESULTS AND DISCUSSION

Ramipril is a white powder slightly soluble in water. In order to reduce the amount of impurities, a weakly alkaline substance with minimized moisture should be used in Ramipril tablets. The concentration of ramipril was fixed at about 3 % m/m based on the available studies [10].

Kollidon® VA 64 and Soluplus® were selected as matrix-forming polymers. Both of these polymers are thermoplastic materials with a low glass transition temperature (101 °C and 70 °C, respectively). The addition of sodium stearyl fumarate lubricant is associated with the difficulty of powder loading into the extruder feeder. The lubricant provides a good mixture flowability and therefore the loading accuracy.

Sodium carbonate was added to form a weakly alkaline pH. The filaments with Soluplus® were too plastic and proved unfit for subsequent printing. The addition of mannitol to the composition made the filament extremely brittle and fragile, which had a negative effect during printing.

The composition № 2 with Kollidon® VA 64 77 % and ramipril 3 % was the most suitable for printing (Table 2). The extrusion process produced a filament with a diameter of 1.75 mm which had the necessary plasticity to avoid its breakage and getting stuck in the print head of the machine. Despite the fact that the extrusion process occurs usually at the temperature about 20–30 °C higher than glass transition temperature of polymer (101 °C), the selection of excipients made it possible to reduce the processing temperature up to 105 °C.

| №  | Ramipril | Kollidon® VA 64 | Soluplus® | PEG 1500 | Na2CO3, a/h | Kollidon® CL-F | Poloxamer 188 | Alubra | Mannitol | Textrusion, °C |
|----|----------|-----------------|-----------|----------|-----------|---------------|----------------|----------|-----------|----------------|
| 1  | 3        | 70              | –         | 15       | 2         | 5             | 3              | 2        | –         | 100            |
| 2  | 3        | 77              | –         | 8        | 2         | 5             | 3              | 2        | –         | 105            |
| 3  | 3        | 56              | 20        | 10       | 2         | 5             | 3              | 1        | –         | 100            |
| 4  | 4        | 77              | –         | 8        | 2         | 5             | 3              | 1        | –         | 105            |
| 5  | 3        | 65              | –         | 20       | 2         | –             | –              | –        | –         | 100            |
| 6  | 3        | –               | 77        | 15       | 5         | –             | –              | –        | –         | 110            |
| 7  | 3        | –               | 82        | 10       | 5         | –             | –              | –        | –         | 100            |
Tablets were printed in 5 variations of infill percentage: 100 %, 50 % with cap (C) and no cap (NC), 30 % with cap (C) and no cap (NC) (Figure 2). A digital model was created in the CAD program, sliced (Figure 3) and sent to the printer.

Figure 2. Pictures of ramipril with different percentage of infill: a – 100 %; b – 50 % C; c – 50 % NC; d – 30 % C; e – 30 % NC

Figure 3. CAD models of tablets with different percentage of infill: 100 %, 50 %, 30 % with brim

The printing parameters ensured a correct geometric shape and homogeneity of the layer thickness of tablets (Figure 4).

Nowadays, there is no regulatory documentation on quality parameters for printed dosage forms. The printlets were tested for friability, hardness and the average weight (Table 3). The printed tablets with 100% infill had a high hardness, the 30 %NC and 30 %C tablets had a relatively low but acceptable hardness. All tablets passed the friability test.

Table 3. Ramipril tablets technological parameters

| Parameter of quality | Printlets |
|----------------------|-----------|
|                      | 100 %     | 50 % C    | 50 % NC   | 30 % C    | 30 % NC   |
| Average mass, g      | 0.208 ± 0.019 | 0.166 ± 0.011 | 0.159 ± 0.012 | 0.142 ± 0.009 | 0.127 ± 0.015 |
| Thickness, mm        | 2.65 ± 0.12  | 2.31 ± 0.03  | 2.32 ± 0.07  | 2.40 ± 0.21  | 2.35 ± 0.11  |
| Diameter, mm         | 10.12 ± 0.12 | 9.98 ± 0.11  | 10.08 ± 0.11 | 10.12 ± 0.17 | 10.03 ± 0.35 |
| Friability, %        | 0.03       | 0.01       | 0.31       | 0          | 0          |
| Hardness, N          | 155.0 ± 17.6 | 46.0 ± 9.3  | 60.0 ± 8.8  | 35.3 ± 9.7  | 23.3 ± 6.7  |
| Ramipril loading, mg | 6.12 ± 0.53 | 5.09 ± 0.24 | 4.77 ± 0.38 | 4.31 ± 0.32 | 3.76 ± 0.49 |

The drug is exposed to a specific temperature for a longer time during the extrusion compared to the printing process. So it is important to evaluate ramipril stability in the filament rather than in tablets. It is evident from the spectral DSC data (Figure 5) that ramipril did not undergo any degradation during extrusion. Hence, ramipril is expected to be stable in the formulations which are composed of 97 % excipients, thereby exhibiting an additional insulating effect on the drug.

The copovidone thermal curve overlaps the melting peak of ramipril, so DSC spectra for the physical mixture and filament are not informative, however, the selected component proportions enable a lower melting point of the blend relative to the melting point of individual Kollidon® VA 64, thus reducing the processing temperature.

Ramipril has a crystalline structure. Raman spectra did not contain typical peaks indicating that the substances in the filament and tables are in crystalline form. Hence, it can be assumed that the melting of polymers with ramipril can lead to the formation of a solid dispersion of ramipril-Kollidon® VA 64-PEG (Figure 6).
The concentration of ramipril in filaments and tablets was determined with HPLC in order to show that ramipril does not degrade at high extrusion and printing temperatures. The loading of ramipril was \((3.05 \pm 0.15)\%\) of the weight of the filaments and 3\% of the weight of the tablets. The loading of ramipril was in the range from 98 to 101\% of the theoretical mass of tablets which allows the manufacture of tablets with the required dosages on-demand.

The dissolution test of printlets was carried out to investigate the release of ramipril from tablets with different infillings. Ramipril in 100\% tablets had the slowest and gradual release (Figure 7). These tablets are printable, have a minimal variation of the average weight and target dosage. The printlets 50 %C and 50 %NC had a similar curve of ramipril release, hence, the tablet’s cap did not influence the ramipril release. Tablets 30 %C provide a consistent release of ramipril.

**CONCLUSION**

FDM printing is an additional production method for generation of personalized dosage forms on-demand. FDM printing was investigated as a method of the development of tablets containing a thermolabile substance (ramipril). The experimental melting point of ramipril was determined. The melting point of

![Figure 5. DSC plot of ramipril](image1)

![Figure 6. Raman spectra of ramipril, physical mixture, filament and tablet](image2)
ramipril is 114 °C, its degradation temperature is 120 °C. The composition of the tablets was selected, and the temperature of the extrusion process should be reduced up to 105 °C, ensuring the stability of ramipril. Ramipril loading in the filaments made up 98–100 % of the theoretical one.

Tablets of 10 mm in diameter were printed from filaments with different infill percentage: 100 %, 50 %, and 30 %, accordingly. The obtained tablets successfully endured the friability test; dosage forms with 100 % filling had the maximum hardness.

The comparison of the release kinetics of ramipril showed that ramipril was released more uniformly and more slowly from the tablets with 100% filling. The 100%-filled tablets were printed easily, had minimal deviations from the average mass and targeted dosage.

Consequently, Kollidon® VA 64 is suitable as a matrix-polymer for the manufacture of immediate-release ramipril tablets. Kollidon® VA 64 provides necessary physical properties of the filament required for FDM printing.

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