DEVELOPMENT OF 3D-PRINTED DOSAGE FORMS WITH RUTIN

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Introduction. Flavonoids are a huge class of phenolic substances. To the date there are around 6000 compounds discovered. They are of great therapeutic importance as antioxidant, antibacterial, antiviral, and anti-inflammatory medicines. Flavonoid-based natural and semi-synthetic drugs are widely represented in the pharmaceutical market for the treatment of venous insufficiency (Diosmin, Troxerutin, Hesperidin), gastric ulcer and gastritis (Eupatilin), and liver disorders (Silibinin). The most of their dosage forms are produced by pharmaceutical industry, but sometimes the conception "one size fits all" is not acceptable. Therefore, process of personalization in medicine is being developed. 3D printing technologies is a promising and attractive area of research in pharmaceutical dosage form development, particularly for the design of personalized treatments [1, 2, 3].

Aim of the study was to develop 3D-printed dosage forms loaded with rutin using semi-solid extrusion (SSE) 3D printing.

Research methods. For preparing the aqueous PEO gels loaded with rutin, rutin (Nanjing NutriHerb BioTech Co, China, purity 95%), tween-80 (Ferak Berlin GmbH, Germany), PEO (MW approx. 900,000, Sigma-Aldrich, USA), ethanol (Peenviinavabrik, Estonia), and distilled water *R* were used at different proportions. The viscosity of gels was determined with a Physica MCR 101 rheometer (Anton Paar, Austria) using a cone-plate geometry. The gel structure and the degree of homogenization were evaluated by means of optical light microscopy (Magtex-T Dual Illum., Medline Scientific, United Kingdom) equipped with a digital camera (Industrial Digital Camera UCMOS09000KPB (9.0 MP 1 / 2.4" APTNA CMOS sensor). The PEO gels loaded with rutin were directly printed using a bench-top SSE 3D printing system (System 30 M, Hyrel 3D, USA) [4, 5]. For verifying a 3D printing quality, a model 4×4 grid lattice was designed with Autodesk 3ds Max Design 2017 software (Autodesk Inc., USA) [6]. The SSE 3D-printed PEO lattices and round-shaped disc preparations were weighed with an analytical scale (Scaltec SBC 33, Scaltec, Germany) and photographed. The photographs were analyzed using mageJ (National Institute of Health, USA) image analysis software (version 1.51k) [6]. The determination of the quantitative content of rutin in the SSE 3D-printed preparations was carried out with a modified high-performance liquid chromatography (HPLC) method using Chromatograph Prominence Modular HPLC (Shimadzu, Japan) and by spectrophotometry.

Main results. Different concentrations of tween-80 were used for preparing PEO gels loaded with rutin. The experimental PEO gels with a concentration of tween-80 of 5% were the most homogeneous and provided great printability. The viscosity of the gels rated from 210200 to 219333 cP (speed 0.03 RPM, shear rate 0.060 1/s, temperature 22 ± 2 °C). The rutin-PEO gels were printed to lattice- and round-shaped solid drug delivery systems (DDSs) with a head speed of 0.5 mm/s, and the weight (mass uniformity) and effective surface area of the printed DDSs were determined. We found that the maximum concentration of rutin loadable in the PEO

gel for SSE 3D printing was 150 mg/mL. The key process parameters of the SSE 3D printing were identified and verified. The printing quality of rutin-PEO DDSs was very good, thus showing the compatibility of a plant-origin substance and a carrier polymer (PEO). The rutin content (%) and content uniformity of the SSE 3D-printed preparations were assayed by means of spectrophotometry and HPLC. The rutin content of 3D-printed preparations studied was close to a theoretical value (i.e., the amount of rutin calculated and added in the aqueous PEO gels), and the content uniformity was very good. The SSE 3D-printed preparations obtained from aqueous PEO gels disintegrated rapidly within 15-20 minutes, suggesting their potential applicability as an oral immediate-release delivery system for rutin.

Conclusions. Novel aqueous PEO gel formulations loaded with plant-origin rutin were developed for pharmaceutical SSE 3D printing. The most feasible aqueous PEO gel formulation for the SSE 3D printing of rutin was composed of rutin 100 mg/ml and tween-80 50 mg/ml dissolved in a 12% aqueous PEO gel. The SSE 3D-printed dosage forms are purposed for the oral administration of rutin.

References.

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